CUK - H05839 - 38 - P25787

BJA

INTERNATIONAL JOURNAL OF ANAESTHESIA

Editor of General Issues
G. SMITH
B.Sc., M.D., F.R.C.A.

Editor of Educational Reviews
L. STRUNIN
M.D., F.R.C.A., F.R.C.P.C.

Volume 76
1996

38

Published by
Professional and Scientific Publications
BMA House
Tavistock Square
London WC1H 9JR

Typeset in Great Britain by
the University Press, Cambridge

P 257,87

CONTENTS

JANUARY

EDITORIAL: Remembrance of times past: the significance of c-*fos* in pain 1
R. Munglani, B. G. Fleming and S. P. Hunt

CLINICAL INVESTIGATIONS

Dobutamine increases oxygen consumption during constant flow cardiopulmonary bypass 5
W. Karzai, A. Lötte, M. Günnicker, U. M. Vorgrimler-Karzai and H.-J. Priebe

Effects of sevoflurane and isoflurane on systemic vascular resistance: use of cardiopulmonary bypass as a study model 9
G. Rödig, C. Keyl, G. Wiesner, A. Philipp and J. Hobbhahn

Cardiopulmonary bypass with modified fluid gelatin and heparin-coated circuits 13
P. G. M. Jansen, H. te Velthuis, W. R. Wildevuur, M. A. J. M. Huybregts, E. R. Bulder, H. I. van der Spoel, A. Sturk, L. Eijsman and C. R. H. Wildevuur

Pupil changes during cardiopulmonary bypass 20
G. C. Fletcher, A. J. Asbury and J. H. Brown

Vecuronium infusion requirements in paediatric patients in intensive care units: the use of acceleromyography. 23
U. M. Hodges

Pharmacokinetics of rocuronium after bolus and continuous infusion during halothane anaesthesia..... 29
E. P. McCoy, R. K. Mirakhur, V. R. Maddineni, J. M. K. H. Wierda and J. H. Proost

Effect of suxamethonium on the auditory evoked response in humans 34
M. D. Brunner, D. Nathwani, P. A. Rich, C. Thornton, C. J. Doré and D. E. F. Newton

Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by evoked potentials......... 38
D. Roth, S. Petersen-Felix, P. Bak, L. Arendt-Nielsen, M. Fischer, P. Bjerring and A. M. Zbinden

Use of near infrared spectroscopy to estimate cerebral blood flow in conscious and anaesthetized adult subjects 43
H. Owen-Reece, C. E. Elwell, W. Harkness, J. Goldstone, D. T. Delpy, J. S. Wyatt and M. Smith

Effect of transdermal hyoscine on nausea and vomiting during and after middle ear surgery under local anaesthesia.. 49
P. Honkavaara

Single dose i.v. tropisetron in the prevention of postoperative nausea and vomiting after gynaecological surgery 54
V. Capouet, C. De Pauw, B. Vernet, D. Ivens, V. Derijcke, L. Versichelen, H. van Aken, B. Ickx, L. Ritter and F. Hulstaert

Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for Caesarean section 61
D. G. Thomas, S. C. Robson, N. Redfern, D. Hughes and R. J. Boys

A double-blind comparison of 0.25% ropivacaine and 0.25% bupivacaine for extradural analgesia in labour. 66
J. M. Eddleston, J. J. Holland, R. P. Griffin, A. Corbett, E. L. Horsman and F. Reynolds

Absence of an early pre-emptive effect after thoracic extra-dural bupivacaine in thoracic surgery 72
J. L. Aguilar, R. Rincón, V. Domingo, P. Espachs, M. J. Preciado and F. Vidal

Prilocaine 3% is superior to a mixture of bupivacaine and lignocaine for peribulbar anaesthesia 77
U. R. Döpfmer, D. G. Maloney, P. A. Gaynor, R. M. H. Ratcliffe and S. Döpfmer

Haemodynamic effects of moderate normovolaemic haemodilution in conscious and anaesthetized patients 81
P. Biboulet, X. Capdevila, D. Benetreau, P. Aubas, F. d'Athis and J. du Cailar

Analysis of ethanol in expired air during low-flow isoflurane anaesthesia 85
J. Olsson and R. G. Hahn

Perioperative mucosal pH and splanchnic endotoxin concentration in orthotopic liver transplantation 90
M. Welte, B. Pichler, J. Groh, M. Anthuber, K.-W. Jauch, E. Pratschke, F.-P. Lenhart, M. Haller, L. Frey and K. Peter

LABORATORY INVESTIGATIONS

Nitrous oxide or halothane, or both, fail to suppress c-*fos* expression in rat spinal cord dorsal horn neurones after subcutaneous formalin.................................. 99
W. Z. Sun, B. C. Shyu and J. Y. Shieh

Effects of morphine on atrial preparations obtained from non-failing and failing human hearts.................. 106
F. Llobel and M. L. Laorden

A perfusion system for *in vitro* measurement of human cilia beat frequency.................................... 111
D. A. Selwyn, A. Gyi, J. H. Raphael, A. Key and J. A. Langton

Effects of 3 MAC of halothane, enflurane and isoflurane on cilia beat frequency of human nasal epithelium *in vitro* 116
J. H. Raphael, D. A. Selwyn, S. D. Mottram, J. A. Langton and C. O'Callaghan

Effect of phosphodiesterase inhibitors on human arteries *in vitro* 122
M. B. Vroom, M. Pfaffendorf, H. B. van Wezel and P. A. van Zwieten

Effect of pneumoperitoneum and Trendelenburg position on gastro-oesophageal reflux and lower oesophageal sphincter pressure 130
J. P. Tournadre, D. Chassard, K. R. Berrada and P. Bouletreau

REVIEW ARTICLE

Recent developments in the pathophysiology and management of pre-eclampsia 133
M. C. Mushambi, A. W. Halligan and K. Williamson

SHORT COMMUNICATIONS

Extradural and subarachnoid catheterization using the Seldinger technique.................................... 149
E. M. Delhaas

Regional anaesthesia for outpatient nasal surgery.......... 151
S. Molliex, M. Navez, D. Baylot, J. M. Prades, Z. Elkhoury and C. Auboyer

Effect of smoking on dose requirements for vecuronium.. 154
H. Teiriä, P. Rautoma and A. Yli-Hankala

CASE REPORTS

Airway problems in carotid endarterectomy............. 156
F. J. Munro, A. P. Makin and J. Reid

Mivacurium chloride and late onset congenital myopathy. 160
M. Parmar and R. P. F. Scott

Anaesthesia and juvenile hyaline fibromatosis 163
B. Norman, N. Soni and N. Madden

CORRESPONDENCE

Visceral pain during Caesarean section............................. 167
Cannabis as a medicine... 167
Naproxen after day-case laparoscopic sterilization.......... 168
Systolic pressure variation—a way to recognize dynamic hyperinflation 168
Intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia 169
RAE tube obstruction during tonsil dissection............... 170
Extradural clonidine for postoperative pain relief........... 171
Porphyria, propofol and rats.. 171

BOOK REVIEWS

Baillières Clinical Anaesthesiology: New Pharmacological Vistas 173
Basics of Transoesophageal Echocardiography 173
Modulation of the Inflammatory Response in Severe Sepsis 173
Sedation and Analgesia in the Critically Ill 174
Anaesthesia: Review 11 174
A Practical Approach to Cardiac Anesthesia 174

Erratum 175

FEBRUARY

EDITORIAL: Prospects for management of peripheral vascular failure in septic shock 177
J. D. Allen and N. A. Herity

CLINICAL INVESTIGATIONS

Effect of age on MAC in humans: a meta-analysis 179
W. W. Mapleson

Omitting nitrous oxide in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials 186
M. Tramèr, A. Moore and H. McQuay

Cognitive failures after general anaesthesia for day-case surgery 194
Y. Tzabar, A. J. Asbury and K. Millar

Use of i.v. insulin in well-controlled non-insulin-dependent diabetics undergoing major surgery 198
M. Raucoules-Aimé, Y. Labib, J. Levraut, P. Gastaud, C. Dolisi and D. Grimaud

Pulmonary uptake of sufentanil during and after constant rate infusion 203
F. Boer, E. Olofsen, J. G. Bovill, A. G. L. Burm, A. Hak, M. Geerts and K. E. Wetselaar

Does pre-incisional thoracic extradural block combined with diclofenac reduce postoperative pain after abdominal hysterectomy? 209
A. Espinet, D. J. Henderson, K. A. Faccenda and L. M. M. Morrison

Influence of oral clonidine on the ventilatory response to acute and sustained isocapnic hypoxia in human males. 214
I. T. Foo, P. M. Warren and G. B. Drummond

Comparison of nicardipine, diltiazem and verapamil for con-trolling the cardiovascular responses to tracheal intubation 221
K. Mikawa, K. Nishina, N. Maekawa and H. Obara

Preoperative infusion of amino acids prevents postoperative hypothermia 227
E. Selldén, R. Brånström and T. Brundin

Time course of potentiation of mivacurium by halothane and isoflurane in children 235
O. A. Meretoja, K. Wirtavuori, T. Taivainen and K. T. Olkkola

Edrophonium antagonism of intense mivacurium-induced neuromuscular block in children 239
M. Abdulatif, A. Al-Ghamdi, M. Al-Sanabary and M. E. Abdel-Gaffar

Fuzzy logic control of inspired isoflurane and oxygen concentrations using minimal flow anaesthesia 245
M. Curatolo, M. Derighetti, S. Petersen-Felix, P. Feigenwinter, M. Fischer and A. M. Zbinden

LABORATORY INVESTIGATIONS

Methylprednisolone inhibits endotoxin-induced depression of contractile function in human arteries *in vitro* 251
I. Tsuneyoshi, Y. Kanmura and N. Yoshimura

Central nuclei and spinal pathways in feedback inhibitory spinal cord potentials in ketamine-anaesthetized rats 258
S. Denda, K. Shimoji, M. Tomita, H. Baba, T. Yamakura, H. Masaki, H. Endoh and S. Fukuda

Relaxant effect of ketamine and its isomers on histamine-induced contraction of tracheal smooth muscle 266
K. Hirota, T. Sato, S. F. Rabito, E. K. Zsigmond and A. Matsuki

Interaction of i.v. anaesthetic agents with 5-HT_3 receptors 271
B. L. Appadu and D. G. Lambert

Effects of morphine on human nasal cilia beat frequency *in vitro* 274
D. A. Selwyn, J. H. Raphael, D. G. Lambert and J. A. Langton

Electromyographic and mechanomyographic characteristics of neuromuscular block by magnesium sulphate in the pig 278
C. Lee, X. Zhang and W.-F. Kwan

A model to describe the rate of oxyhaemoglobin desaturation during apnoea 284
A. D. Farmery and P. G. Roe

Nitrous oxide and the rate of gas uptake from an unventilated lung in dogs 292
C. J. Joyce, A. B. Baker, R. Parkinson and M. Zacharias

Interpleural local anaesthesia: anatomical basis for mechanism of action 297
A. G. McKenzie and S. Mathe

REVIEW ARTICLE

Ropivacaine 300
J. H. McClure

SHORT COMMUNICATIONS

Dose of propofol for laryngeal mask airway insertion in children: effect of premedication with midazolam 308
R. A. Martlew, G. Meakin, R. Wadsworth, A. Sharples and R. D. Baker

Comparison of i.v. and s.c. diamorphine infusions for the treatment of acute pain in children 310
D. Semple, L. A. Aldridge and E. Doyle

Prospective evaluation of pharmacokinetic model-controlled infusion of propofol in adult patients 313
T. G. Short, T. A. Lim and Y. H. Tam

Effect of ondansetron on nausea and vomiting after middle ear surgery during general anaesthesia 316
P. Honkavaara

Extradural analgesia with clonidine and fentanyl compared with 0.25% bupivacaine in the first stage of labour 319
D. J. Buggy and C. MacDowell

CASE REPORTS

Sudden onset of subarachnoid block after subdural catheterization: a case of arachnoid rupture? 322
D. W. Elliott, F. Voyvodic and P. Brownridge

Elective forceps delivery and extradural anaesthesia in a primigravida with portal hypertension and oesophageal varices 325
J. A. Heriot, C. M. Steven and R. S. Sattin

Bilateral severe pain at L3–4 after spinal anaesthesia with hyperbaric 5% lignocaine 328
R. Rodríguez-Chinchilla, A. Rodríguez-Pont, T. Pintanel and F. Vidal-López

Pulsed saline lavage causing venous air embolism in a patient with Paget's disease 330
C. A. Sides

CORRESPONDENCE

Inadvertent infusion of glucose saline into the extradural space 332
Cardiac arrest at induction of anaesthesia for Caesarean section 332
Day-case cataract surgery 333
Effects of propofol on rabbit mesenteric arteries and veins 333
A pitfall in the use of the Altman nomogram for power estimation 334
Change in neostigmine ampoules 334
Volume preloading, spinal anaesthesia and Caesarean section 334
Accidental insertion of an extradural catheter 336
Transoesophageal echocardiography in chest trauma 336

BOOK REVIEWS

Anaesthesia and Critical Care Manual, 2nd Edn 338
Anaesthesia and Intensive Care for Patients with Liver Disease 338
Principles and Practice Series: Respiratory Support 338
The ABC of Resuscitation, 3rd Edn 338

Erratum 339

MARCH

EDITORIALS:

I: Remifentanil—an opioid for the 21st century 341
J. P. Thompson and D. J. Rowbotham
II: Voltage-sensitive Ca^{2+} channels and anaesthesia 344
K. Hirota and D. G. Lambert

CLINICAL INVESTIGATIONS

Prediction of postoperative nausea and vomiting using a logistic regression model 347
C. C. Toner, C. J. Broomhead, I. H. Littlejohn, G. S. Samra, J. G. Powney, M. G. A. Palazzo, S. J. W. Evans and L. Strunin
Metabolic and hormonal responses to induced hypotension for middle ear surgery 352
M. C. Newton, G. D. Chadd, B. O'Donoghue, S. M. Sapsed-Byrne and G. M. Hall
Influence of dose and timing of administration of morphine on postoperative pain and analgesic requirements 358
M. D. Mansfield, K. S. James and J. Kinsella
Recovery after desflurane anaesthesia in the infant: comparison with isoflurane 362
A. R. Wolf, R. A. Lawson, C. M. Dryden and F. W. Davies
Perioperative changes in α_1-acid glycoprotein concentrations in infants undergoing major surgery 365
P. D. Booker, C. Taylor and G. Saba
Changes in chest wall compartment volumes on induction of anaesthesia with eltanolone, propofol and thiopentone 369
H. J. Spens, G. B. Drummond and P. K. Wraith
Slow ventilatory dynamics after isocapnic hypoxia and voluntary hyperventilation in humans: effects of isoflurane 374
A. Dahan, J. van Kleef, M. van den Elsen, R. Valk and A. Berkenbosch
Comparison of the pharmacodynamics and pharmacokinetics of an infusion of *cis*-atracurium (51W89) or atracurium in critically ill patients undergoing mechanical ventilation in an intensive therapy unit ... 382
A. H. Boyd, N. B. Eastwood, C. J. R. Parker and J. M. Hunter
Effect of isoflurane and sevoflurane on the magnitude and time course of neuromuscular block produced by vecuronium, pancuronium and atracurium 389
L. E. H. Vanlinthout, L. H. D. J. Booij, J. van Egmond and E. N. Robertson
Performance assessment of a fuzzy controller for atracurium-induced neuromuscular block 396
D. G. Mason, N. D. Edwards, D. A. Linkens and C. S. Reilly
Comparison of arterialized venous with arterial blood propofol concentrations during sub-anaesthetic infusions in volunteers 401
K. R. Johnston, M. D. Vickers and W. W. Mapleson
Radial artery tonometry: moderately accurate but unpredictable technique of continuous non-invasive arterial pressure measurement 405
B. M. Weiss, D. R. Spahn, H. Rahmig, R. Rohling and T. Pasch
Haemodilution induces a hypercoagulable state 412
T. G. Ruttmann, M. F. M. James and J. F. Viljoen
Effect of tramadol on depth of anaesthesia 415
J. F. Coetzee, J. S. Maritz and J. C. du Toit

LABORATORY INVESTIGATIONS

Effects and interactions of myocardial ischaemia and alterations in circulating blood volume on canine left ventricular diastolic function 419
S. Dalmas, S. C. U. Marsch, D. M. Philbin, D. J. Gavaghan, W. A. Ryder and P. Foëx
Effects of carbon dioxide embolism with nitrous oxide in the inspired gas in piglets 428
J.-B. Nyarwaya, S. Pierre, J.-X. Mazoit, V. Umbrain, M. Romain, K. Samii and A. d'Hollander

REVIEW ARTICLE

Sevoflurane—a long-awaited volatile anaesthetic 435
I. Smith, M. Nathanson and P. F. White

SHORT COMMUNICATIONS

Effect of neuromuscular block on depth of anaesthesia as measured by the auditory evoked response 446
C. E. Richmond, A. Matson, C. Thornton, C. J. Doré and D. E. F. Newton
Comparison of ondansetron and prochlorperazine for the prevention of nausea and vomiting after adenotonsillectomy 449
A. A. van den Berg
Smaller children have greater bupivacaine plasma concentrations after ilioinguinal block 452
T. Smith, P. Moratin and H. Wulf
Laryngeal mask airway performance: effect of cuff deflation during anaesthesia 456
G. N. Morris and R. Marjot
Delayed forced air warming prevents hypothermia during abdominal aortic surgery 459
J. Karayan, D. Thomas, L. Lacoste, K. Dhoste, J. B. Ricco and J. Fusciardi
Fentanyl increases intracelluar Ca^{2+} concentrations in SH-SY5Y cells 461
A. L. Wandless, D. Smart and D. G. Lambert

CASE REPORTS

Myocardial ischaemia associated with Ehlers-Danlos syndrome 464
C. M. Price, S. Ford, L. St John Jones and V. Murday
Reducing the potential morbidity of an unintentional spinal anaesthetic by aspirating cerebrospinal fluid.... 467
P. Southorn, G. M. S. Vasdev, R. C. Chantigian and G. M. Lawson

COMMENTARY

Consensus statement on autologous transfusion 470

CORRESPONDENCE

Histamine release by neuromuscular blocking agents.... 471
Preoperative fasting for paediatric anaesthesia 471
Use of i.m. temperature probes during cardiopulmonary bypass in humans 471
EEG arousal during laryngoscopy and intubation 472
Venous thromboembolism and cardiovascular surgery.... 473
Prevention of vomiting after paediatric strabismus surgery 473
Maternal sequelae of childbirth 474
Venous air embolism: is end-tidal oxygen monitoring more informative than end-tidal carbon dioxide? 475
Spinal anaesthesia for Caesarean section in women with incomplete extradural analgesia 476

BOOK REVIEWS

Primer of Intraoperative Neurophysiologic Monitoring 477
Wylie & Churchill-Davidson's A Practice of Anaesthesia, 6th Edn 477

APRIL

EDITORIALS:

I: The 11th World Congress of Anaesthesiology 479
G. Smith
II: Rocuronium: the newest aminosteroid neuromuscular blocking drug 481
J. M. Hunter

CLINICAL INVESTIGATIONS

Dose requirements, efficacy and side effects of morphine and pethidine delivered by patient-controlled analgesia after gynaecological surgery............................ 484
G. Stanley, B. Appadu, M. Mead and D. J. Rowbotham

Postoperative analgesia by continuous extradural infusion of ropivacaine after upper abdominal surgery 487
S. A. Schug, D. A. Scott, J. Payne, P. H. Mooney and B. Hägglöf

Is there implicit memory after propofol sedation? 492
R. C. Cork, J. F. Heaton, C. E. Campbell and J. F. Kihlstrom

Activation of the electrocorticogram by propofol during surgery for epilepsy 499
M. Smith, S. J. Smith, C. A. Scott and W. F. J. Harkness

Periodic cardiovascular and ventilatory activity during midazolam sedation 503
D. C. Galletly, T. B. Williams and B. J. Robinson

Anatomical configuration of the spinal column in the supine position. III. Comparison of adolescent and adult volunteers 508
Y. Hirabayashi, R. Shimizu, K. Saitoh, H. Fukuda, T. Igarashi and M. Furuse

Convective warming combined with vasodilator therapy accelerates core rewarming after coronary artery bypass surgery 511
S. J. Harrison and J. Ponte

Single-dose i.v. granisetron in the prevention of postoperative nausea and vomiting 515
A. J. Wilson, P. Diemunsch, B. G. Lindeque, H. Scheinin, H. S. Helbo-Hansen, M. V. A. M. Kroeks and K. L. Kong

Rheological properties of commonly used . plasma substitutes during preoperative normovolaemic acute haemodilution 519
G. Freyburger, M. Dubreuil, M. R. Boisseau and G. Janvier

Rocuronium pretreatment reduces suxamethonium-induced myalgia: comparison with vecuronium 526
G. P. Findlay and M. J. Spittal

Carbon dioxide output in laparoscopic cholecystectomy 530
T. Kazama, K. Ikeda, T. Kato and M. Kikura

LABORATORY INVESTIGATIONS

Effect of propofol and thiopentone on free radical mediated oxidative stress of the erythrocyte 536
P. G. Murphy, M. J. Davies, M. O. Columb and N. Stratford

Antinociceptive actions of intrathecal xylazine: interactions with spinal cord opioid pathways 544
C. S. Goodchild, Z. Guo, A. Davies and J. P. Gent

REVIEW ARTICLE

Postoperative sleep disturbances: mechanisms and clinical implications 552
S. Rosenberg-Adamsen, H. Kehlet, C. Dodds and J. Rosenberg

SHORT COMMUNICATIONS

Effect of apparatus on functional residual capacity 560
G. B. Drummond

Measurement technique and variation in intramucosal pH 563
P. R. Wood and P. G. P. Lawler

Magnesium sulphate enhances residual neuromuscular block induced by vecuronium 565
T. Fuchs-Buder and E. Tassonyi

Comparison of the effect of two dose schedules of oral omeprazole with oral ranitidine on gastric aspirate pH and volume in patients undergoing elective surgery... 567
I. D. Levack, R. A. Bowie, D. P. Braid, A. J. Asbury, R. L. Marshall, K. B. Slawson, H. Birrell and K. R. W. Gillon

CASE REPORTS

Unilateral convulsion after induction of anaesthesia with propofol... 570
D. Cochran, W. Price and C. L. Gwinnutt

Airway management for patients with a tracheal bronchus 573
S. Ikeno, H. Mitsuhata, K. Saito, Y. Hirabayashi, S. Akazawa, H. Kasuda and R. Shimizu

ABSTRACTS

Proceedings of the Anaesthetic Research Society, Manchester Meeting, November 23–24, 1995 .... 576P

CORRESPONDENCE

Psychological characteristics and patient-controlled analgesia 595
Ulnar and common peroneal nerve block revisited 595
Nebulized lignocaine before gaseous induction with desflurane.. 596
Factors governing onset of neuromuscular block 596
Effects of propofol and isoflurane on right ventricular function 598

Erratum 598

BOOK REVIEWS

Neuro-anaesthetic Practice 599
Intensive Care: A Concise Textbook, 2nd Edn 599
Handbook of Neonatal Anaesthesia 599

MAY

EDITORIALS: I: Perioperative inadvertent hypothermia: what do we need to prevent? 601
F. Carli and I. A. MacDonald
II: Gastric tonometry to monitor tissue oxygenation: more than a gut feeling? . 604
T. E. Oh

CLINICAL INVESTIGATIONS

Continuous extradural infusion of ropivacaine for prevention of postoperative pain after major orthopaedic surgery 606
G. Turner, D. Blake, M. Buckland, D. Chamley, P. Dawson, C. Goodchild, J. Mezzatesta, D. Scott, A. Sultana, S. Walker, M. Hendrata, P. Mooney and M. Armstrong

Patient-controlled extradural analgesia with bupivacaine, fentanyl, or a mixture of both, after Caesarean section 611
D. W. Cooper, D. M. Ryall, F. E. McHardy, S. L. Lindsay and S. S. Eldabe

Maternal and uteroplacental haemodynamic state in pre-eclamptic patients during spinal anaesthesia for Caesarean section 616
J. Karinen, J. Räsänen, S. Alahuhta, R. Jouppila and P. Jouppila

Effect of antagonism of mivacurium on recovery of extraocular muscle function 621
D. J. Mellor, E. Moss, E. M. McAteer and M. V. Shah

Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation... 624
A. M. De Wolf, J. A. Freeman, V. L. Scott, W. Tullock, D. A. Smith, D. F. Kisor, S. Kerls and D. Ryan Cook

Soluble E-cadherin concentrations in patients with systemic inflammatory response syndrome and multi-organ dysfunction syndrome........................... 629
A. J. Pittard, R. E. Banks, H. F. Galley and N. R. Webster

Preoperative inhibition of angiotensin-converting enzyme improves systemic and renal haemodynamic changes during aortic abdominal surgery.......................... 632
M. Licker, M. Bednarkiewicz, P. Neidhart, R. Prêtre, M. Montessuit, H. Favre and D. R. Morel

Laparoscopic cholecystectomy: haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position 640
E. O'Leary, K. Hubbard, W. Tormey and A. J. Cunningham

Comparisons of the effects of urapidil and sodium nitroprusside on haemodynamic state, myocardial metabolism and function in patients during coronary artery surgery. 645
J. G. van der Stroom, H. B. van Wezel, I. Vergroesen, J. E. Kal, J. J. Koolen, J. P. Dijkhuis, A. Swaan, M. Porsius, H. A. J. Kleinjans and P. A. van Zwieten

Kinetics of methaemoglobin and serum nitrogen oxide production during inhalation of nitric oxide in volunteers 652
J. D. Young, J. W. Sear and E. M. Valvini

Heart rate variability in patients recovering from general anaesthesia 657
N. Ireland, J. Meagher, J. W. Sleigh and J. D. Henderson

Comparison of sedation with midazolam and ketamine: effects on airway muscle activity 663
G. B. Drummond

Accumulation of foreign gases during closed-system anaesthesia 668
L. Versichelen, G. Rolly and H. Vermeulen

A new tracheal tube for difficult intubation 673
M. R. J. West, M. M. Jonas, A. P. Adams and F. Carli

Failed intubation revisited: 17-yr experience in a teaching maternity unit 680
L. Hawthorne, R. Wilson, G. Lyons and M. Dresner

Haemodynamic responses to incision and sternotomy in relation to the auditory evoked potential and spontaneous EEG 685
N. A. M. de Beer, J. C. van Hooff, P. J. M. Cluitmans, H. H. M. Korsten and R. J. E. Grouls

Double-blind, randomized trial of cessation of smoking after audiotape suggestion during anaesthesia 694
P. S. Myles, M. Hendrata, Y. Layher, N. J. Williams, J. L. Hall, J. T. Moloney and J. Powell

Recall during intermittent propofol anaesthesia 699
O. Nordström and R. Sandin

LABORATORY INVESTIGATIONS

Volatile anaesthetics antagonize nitrous oxide and morphine-induced analgesia in the rat 702
T. Goto, J. J. A. Marota and G. Crosby

Effect of low-dose dopamine on intestinal villus microcirculation during normotensive endotoxaemia in rats. 707
H. Schmidt, A. Secchi, R. Wellmann, H. Böhrer, A. Bach and E. Martin

Early effects of total hepatectomy on haemodynamic state and organ uptake of catecholamines in the pig 713
M. F. M. James, R. Hickman, P. Janicki, B. Mets and J. Fourie

Sevoflurane, enflurane and isoflurane have no persistent postanaesthetic effects on the central nervous system in cats 721
J. Kurata, T. Adachi, S. Nakao, M. Murakawa, T. Shichino, M. Shibata and K. Mori

REVIEW ARTICLE

Prehospital monitoring of trauma patients: experience of a helicopter emergency medical service 726
A. P. Morley

SHORT COMMUNICATIONS

Hydroxyethylstarch compared with modified gelatin as volume preload before spinal anaesthesia for Caesarean section 731
M. P. Vercauteren, V. Hoffmann, H. C. Coppejans, A. L. Van Steenberge and H. A. Adriaensen

Hypotension during subarachnoid anaesthesia: haemodynamic effects of colloid and metaraminol 734
L. A. H. Critchley and F. Conway

Interference of volatile anaesthetics with infrared analysis of carbon dioxide and nitrous oxide tested in the Dräger Cicero EM using sevoflurane 737
A. R. Wilkes and W. W. Mapleson

CASE REPORT

Use of recombinant human erythropoietin to facilitate liver transplantation in a Jehovah's Witness 740
N. J. Snook, H. A. O'Beirne, S. Enright, Y. Young and M. C. Bellamy

EQUIPMENT

Validation of the Edslab dual lumen oximetry catheter for continuous monitoring of jugular bulb oxygen saturation after severe head injury 744
M. J. Souter and P. J. D. Andrews

CORRESPONDENCE

Ventilatory response to carbon dioxide 747
Improving preoxygenation 748
Serotonin in pre-eclampsia 748
Cost of volatile agents 749
Effect of transdermal hyoscine on nausea and vomiting. 749
Gastric tonometry 750
Measurement of competence 750

BOOK REVIEWS

600 MCQs in Anaesthesia: Clinical Practice, 2nd Edn 751
Regional Anesthesia: An Atlas of Anatomy and Techniques. 751
Essentials of Anaesthetic Equipment 751

JUNE

EDITORIALS: I: Impact factors in anaesthesia journals 753
G. Smith
II: Airway management in cleft lip and palate surgery 755
D. J. Hatch

CLINICAL INVESTIGATIONS

Difficult laryngoscopy in cleft lip and palate surgery 757
R. H. Gunawardana

Volumetric analysis of aeration in the lungs during general anaesthesia 760
A. Reber, G. Engberg, B. Sporre, L. Kviele, H.-U. Rothen, G. Wegenius, U. Nylund and G. Hedenstierna

Sevoflurane–nitrous oxide or halothane–nitrous oxide for paediatric bronchoscopy and gastroscopy 767
O. A. Meretoja, T. Taivainen, L. Räihä, R. Korpela and K. Wirtavuori

Cricoid pressure applied after placement of the laryngeal mask prevents gastric insufflation but inhibits ventilation 772
T. Asai, K. Barclay, C. McBeth and R. S. Vaughan

Effects of surgical skin incision on respiration in patients anaesthetized with enflurane 777
R. W. Sutherland and G. B. Drummond

Efficiency of a circle system for short surgical cases: comparison of desflurane with isoflurane 780
D. J. H. Lee, D. L. Robinson and N. Soni

Oxygen consumption and delivery relationship in brain-dead organ donors 783
O. Langeron, P. Couture, J. Mateo, B. Riou, J.-L. Pansard and P. Coriat

Sepsis-induced vasoparalysis does not involve the cerebral vasculature: indirect evidence from autoregulation and carbon dioxide reactivity studies 790
B. F. Matta and P. J. Stow

Remifentanil reduces auditory and somatosensory evoked responses during isoflurane anaesthesia in a dose-dependent manner 795
I. Crabb, C. Thornton, K. M. Konieczko, A. Chan, R. Aquilina, N. Frazer, C. J. Doré and D. E. F. Newton

Effect of the addition of alfentanil to lignocaine during axillary brachial plexus anaesthesia 802
W. P. Gormley, J. M. Murray, J. P. H. Fee and S. Bower

Analgesic and anti-inflammatory effects of lignocaine–prilocaine (EMLA) cream in human burn injury 806
J. L. Pedersen, T. Callesen, S. Møiniche and H. Kehlet

Continuous extrapleural paravertebral infusion of bupivacaine for post-thoracotomy analgesia in young infants ... 811
M. K. Karmakar, P. D. Booker, R. Franks and M. Pozzi

Surgical pain is followed not only by spinal sensitization but also by supraspinal antinociception ... 816
O. H. G. Wilder-Smith, E. Tassonyi, C. Senly, Ph. Otten and L. Arendt-Nielsen

Haemostatic changes caused by i.v. regional anaesthesia with lignocaine ... 822
T. T. Niemi, A. H. Kuitunen, E. M. Vahtera and P. H. Rosenberg

Effect of systemic *N*-methyl-D-aspartate receptor antagonist (ketamine) on primary and secondary hyperalgesia in humans ... 829
S. Ilkjaer, K. L. Petersen, J. Brennum, M. Wernberg and J. B. Dahl

Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting ... 835
L. López-Olaondo, F. Carrascosa, F. J. Pueyo, P. Monedero, N. Busto and A. Sáez

LABORATORY INVESTIGATIONS

Differential effects of desflurane and halothane on peripheral airway smooth muscle ... 841
A. J. Mazzeo, E. Y. Cheng, Z. J. Bosnjak, R. L. Coon and J. P. Kampine

Halothane and potassium channels in airway smooth muscle ... 847
T. Fukushima, A. Hirasaki, K. A. Jones and D. O. Warner

Recovery of respiratory ciliary function after depression by inhalation anaesthetic agents: an *in vitro* study using nasal turbinate explants ... 854
J. H. Raphael, J. Strupish, D. A. Selwyn, H. C. L. Hann and J. A. Langton

Effect of halothane on myocardial reoxygenation injury in the isolated rat heart ... 860
W. Schlack, M. Hollmann, J. Stunneck and V. Thämer

SHORT COMMUNICATIONS

Occupational x-ray exposure of anaesthetists ... 868
C. McGowan, B. Heaton and R. N. Stephenson

Total i.v. anaesthesia for transcranial magnetic evoked potential spinal cord monitoring ... 870
J. W. H. Watt, M. H. Fraser, B. M. Soni, P. K. Sett and R. Clay

Spinal clonidine produces less urinary retention than spinal morphine ... 872
M. Gentili and F. Bonnet

Removal of the laryngeal mask airway in children: anaesthetized compared with awake ... 874
A. J. Kitching, A. R. Walpole and C. E. Blogg

CASE REPORTS

Fracture of the cricoid cartilage after Sellick's manoeuvre ... 877
K. J. Heath, M. Palmer and S. J. Fletcher

Balloon mitral valve dilatation as an aid to weaning from ventilatory support in patients with intractable pulmonary oedema caused by severe mitral stenosis ... 879
G. Davis, R. M. Khan, N. Randall, J. S. Wright and D. H. Roberts

CORRESPONDENCE

Suxamethonium and auditory evoked potentials ... 881
Extradural clonidine for postoperative pain relief ... 881
Aprotinin during liver transplantation ... 882
Aortic stent surgery ... 882
Suxamethonium in children ... 883
Isolated forearm technique ... 884
CSF progesterone concentrations in pregnancy ... 886
Extradural analgesia in the first stage of labour ... 886
Extradurals and infection ... 887
Cervical haematoma and airway obstruction ... 888
Management of pre-eclampsia ... 889

Erratum ... 890

BOOK REVIEWS

Anesthesiology, House Officer Series ... 891
Ophthalmic Anaesthesia—A Practical Handbook, 2nd Edn ... 891
Difficult Hypertension: Practical Management and Decision Making ... 891
Acute Pain Management: A Practical Guide ... 892
Anaesthesia for Surgery of the Spine ... 892
Understanding Anaesthesia, 3rd Edn ... 892
Neuromuscular Block ... 893
A Physician's Guide to the Internet ... 893

Index to Volume 76 ... 895

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 76, No. 1 JANUARY 1996

EDITORIAL

Remembrance of times past: the significance of c-*fos* in pain

"Everlasting layers of ideas, images, feelings have fallen upon your brain..., Each succession has seemed to bury all that went before. And yet in reality not one has been extinguished..."

Thomas de Quincey

Advances in neurobiology have provided us with the tools to identify the molecular events that underlie functional and structural change within the nervous system. Examining the molecular responses to nerve stimulation and injury have led not only to an increased understanding of the biological basis of acute and chronic pain states, but also suggest a molecular memory for painful stimulation. One particular molecular marker, c-*fos*, has been the focus of much research after the key observation that painful, but not innocuous, peripheral stimulation rapidly causes the expression of c-*fos* gene expressions within the spinal cord [1]. The article by Sun, Shyu and Shieh [2] in this issue of the journal demonstrates that apparently adequate anaesthesia fails to prevent expression of an immediate early gene "c-*fos*" within the spinal cord after painful peripheral stimulation. In this editorial, clinical consequences of this observation are discussed in relation to the fundamental role of c-*fos* in linking short-term stimuli to long-term structural change within the nervous system.

Immediate early genes such as v-*fos* (viral-*fos*) were first shown to be capable of inducing cell proliferation and were subsequently known as proto-oncogenes. When the same gene was then described in cells it was termed c-*fos* (cellular-*fos*). More than 100 immediate early genes are now known and have fundamental roles in cell proliferation, differentiation and programmed cell death [3]. The basic property shared by all is that they are capable of being induced (i.e. their messenger RNA is produced) without prior protein synthesis, typically within minutes after stimulation. This observation indicates that the cellular machinery required to effect gene transcription is in a state of readiness and contrasts with the "late response genes" which do require further *de novo* protein synthesis before their transcription can be altered. Immediate early genes were shown to form part of the signal transduction cascade from the cell surface to the nucleus leading to long-term changes in structure and function (i.e. plastic changes) and hence were given the title of "*third messengers*" [4] (fig. 1). Studies using Fos showed that its appearance could be used to mark those cells that had been stimulated and activated [5]. Indeed Fos expression has been used to map pathways of activation after various types of peripheral stimulation and generally shows good correlation with known anatomical pathways, for example Fos activation in the spinal cord and brain after noxious stimulation matches known routes which carry pain sensation [6]. As Fos activation can be seen only if sufficient stimulation has occurred in a cell, then it is obvious that Fos activation can be used not only to map metabolic activity in cells but also the effectiveness of therapies to suppress the activity of cells, for example to examine the efficacy of drugs such as those that may prevent secondary brain injury, antiepileptics and analgesics. One advantage of Fos expression over standard neurophysiological techniques is that the responses of large numbers of cells can be assessed as one may examine a whole section of brain or spinal cord for Fos protein or mRNA.

In this issue of the journal, Sun, Shyu and Shieh [2] show that 2% halothane with or without nitrous oxide and the μ agonist, fentanyl, reduced pain-related behaviour in response to painful stimulation but fentanyl alone reduced Fos expression in the spinal cord. The study raises a number of points.

(1) Using Fos expression as an index, volatile agents and nitrous oxide are not adequate analgesics for painful stimulation. However, one could argue that as long as the subject is anaesthetized with the volatile agent and not apparently responding, does it matter that peripheral stimulation reaches the spinal cord and the brain and causes Fos expression? To answer this point we need to know if there is any evidence that using different types of anaesthetic regimens can have long-term consequences for the individual.

(2) Even the large dose of fentanyl only reduced Fos expression by up to 50% in this study, that is significant Fos expression still occurred; if Fos expression were associated with deleterious physiological effects, should we be using other techniques or agents that are more effective at suppressing Fos expression than opioids?

Regarding the first point, there is increasing evidence that pain intensity and duration in acute and chronic pain models can be reduced and perhaps prevented if painful stimulation is impeded from reaching the cord either by the use of prior local anaesthesia or systemic analgesics but not by volatile agents alone [7–9]. In one study, different types of analgesic regimens were tested for their ability to

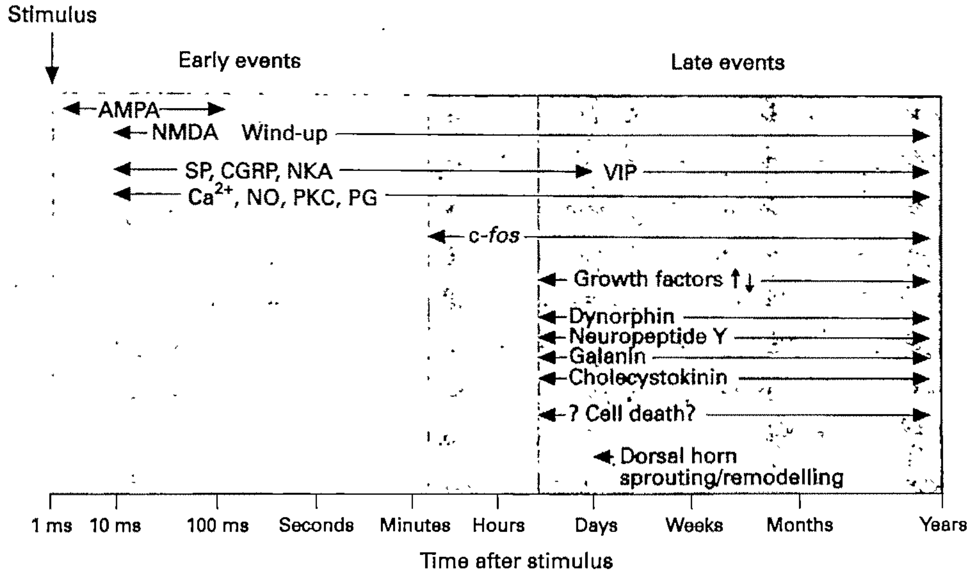


Figure 1 Schematic and partially speculative diagram outlining the cascade of molecular events which may follow peripheral nerve injury or stimulation, which attempts to place in context the role of *c-fos* in this cascade. Some of the changes only occur in certain situations, for example VIP and cholecystokinin are upregulated after peripheral nerve injury but not after inflammatory injury, while others show opposite changes, for example SP increases in inflammatory pain states but decreases after nerve injury. However, many changes are common to both pain states, for example activation of the NMDA channel, increase in intracellular Ca^{2+}, involvement and upregulation of neuronal nitric oxide synthase and increase in *c-fos*. Dynorphin and NPY increases have also been described in both types of pain, and there is some evidence that *c-fos* may lead to their activation. These changes in ion channel function, second messengers, immediate early genes such as *c-fos* ("third messengers") and neuropeptides may then be followed by more permanent changes in the nervous system consisting of changes in synaptic efficacy of pre-existing synapses, nerve sprouting and formation of novel synapses to which *c-fos* may also contribute via growth factors. We speculate that these latter changes may be the basis of pain memories in the spinal cord and brain. There is some evidence that inhibiting the earlier events may delay and perhaps prevent some of the later events, that is prevent the formation of long-term changes which are associated with persistent pain. For further general discussions see [10, 11, 31, 32, 35–40] and references within. AMPA = alpha-amino-3-hydroxy-5-methyl-isoxazole, NMDA = *N*-methyl-D-aspartate, SP = substance P, CGRP = calcitonin gene-related peptide, NKA = neurokinin A, NO = nitric oxide, PKC = protein kinase C, PG = prostaglandins, VIP = vasoactive intestinal polypeptide. Figure redrawn and modified from [41].

prevent the development of a chronic pain state after nerve injury [10]. The use of isoflurane alone was compared with isoflurane with either morphine, an α_2 agonist (clonidine) or an NMDA antagonist (MK-801). Volatile agent alone or morphine pretreatment was not as effective as pretreatment with clonidine or MK-801 in preventing chronic pain behaviour and associated changes in the spinal cord and dorsal root ganglia. Yet all of the regimens seemed equally effective at producing an apparently satisfactory state of anaesthesia at the time of nerve injury. Other studies have shown that α_2 agonists or NMDA antagonist are, in general, more effective than opioids in suppressing Fos expression after peripheral stimulation, although the type of stimulation used is an important factor [11]. Thus the efficacy of analgesics to suppress Fos parallels their ability to prevent the development of a chronic pain state.

Timing of the analgesia is also critical. In acute and chronic pain models, the application of local or systemic analgesia *after* painful stimulation is neither effective in preventing acute or chronic pain nor in suppressing the Fos response [9, 12], hence the concept of pre-emptive analgesia is again supported by these studies. In humans unfortunately, the case for prior administration of analgesics is not as clear-cut; there are only a few clinical studies showing that pre-emptive use of analgesics provides a reduction in subsequent pain perception [9, 13–20]. This is puzzling and yet, as we have suggested previously, analysis of Fos expression may provide some clues [21]. Even very high-dose opioids are not as efficacious as other analgesics in preventing Fos expression and subsequent pain [2, 10, 22, 23]. As clinical studies examining pre-emptive analgesia often use opioids, it may not be that surprising that the pre-emptive analgesia effect is often small or not significant. Another reason may be that again, as suggested previously [21], the duration of the injury outlasts the effective analgesia, for example local anaesthetic block may have worn off while the discharge from the sensitized primary afferent fibres continues minimizing the beneficial effect of the original procedure (see [24–26]).

On one level, Fos can be used simply as a marker of nociception but recent studies have made physiological consequences of Fos expression clearer. Fos may act on many genes to cause their expression, including that of preprodynorphin, neuropeptide Y (NPY) and nerve growth factor [4]. Both dynorphin and NPY have analgesic properties and so Fos may not only signal the magnitude of the insult reaching the spinal cord but also mediate some of its adaptive responses to it. In fact, one can now envisage a cascade of molecular events in the spinal cord after peripheral stimulation leading eventually to permanent structural changes within the nervous system (see fig. 1) [27–32].

In summary, the findings of Sun, Shyu and Shieh and other studies are as follows [2, 9–12, 22].

(1) An anaesthetic regimen based solely on oxygen–nitrous oxide and a volatile agent is not sufficient analgesia for painful stimulation despite the fact that during the procedure there may be no obvious subjective responses. In fact, as far as the spinal cord is concerned, it is totally unprotected against these painful insults which may have consequences for the perception of acute postoperative pain and the development of chronic pain states.

(2) Although most anaesthetists do provide some analgesia at some stage of the operation, pre-emptive local anaesthetic block or analgesic administration which is then continued into the postoperative period is likely to be most beneficial.

(3) The differential effects of various analgesics on Fos expression suggest that the use of other analgesics (such as clonidine, an α_2 agonist, and ketamine, an NMDA antagonist) should be considered, certainly as adjuncts to morphine.

Suggestions that providing operating conditions in which the transmission of peripheral stimulation into the central nervous system is impeded are not new [33, 34]. However, as we have suggested previously, studies using Fos expression in the spinal cord may provide a more rational basis in designing novel pre-emptive anaesthetic regimens.

R. MUNGLANI
University Department of Anaesthesia
University of Cambridge Clinical School
Addenbrooke's Hospital
Hills Road, Cambridge CB2 2QQ
B. G. FLEMING
Norfolk and Norwich Hospital
Brunswick Road, Norwich NR1 3SR
S. P. HUNT
Division of Neurobiology
Laboratory of Molecular Biology
MRC Centre
Hills Road, Cambridge CB2 2QH

References

1. Hunt SP, Pini A, Evan G. Induction of *c-fos* like protein in spinal cord neurones following sensory stimulation. *Nature (London)* 1987; **328**: 632–634.
2. Sun WZ, Shyu BC, Shieh JY. Nitrous oxide or halothane, or both, fail to suppress *c-fos* expression in rat spinal cord dorsal horn neurones after subcutaneous formalin. *British Journal of Anaesthesia* 1996; **76**: 99–105.
3. Evans GI. Immediate–early genes—how immediate and why early? In: Tolle TR, Schadrack J, Zieglgansberger W, eds. *Immediate Early Genes in the Central Nervous System*. Berlin: Springer, 1995; 1–17.
4. Morgan JI, Curran T. Stimulus–transcription coupling in the nervous system: involvement of the inducible proto-oncogenes fos and jun. *Annual Review of Neuroscience* 1991; 14: 421–451.
5. Sagar SM, Sharp FR, Curran T. Expression of *c-fos* protein in brain: metabolic mapping at the cellular level. *Science* 1988; **240**: 1328–1331.
6. Bullitt E. Somatotropy of spinal nociceptive processing. *Journal of Comparative Neurology* 1991; **312**: 279–290.
7. Dickenson A, Sullivan A. Subcutaneous formalin-induced activity of dorsal horn neurones in the rat: differential response to an intrathecal opiate administered pre or post formalin. *Pain* 1987; **30**: 349–360.
8. Seltzer Z, Beilin B, Ginzburg R, Paran Y, Shimko T. The role of injury discharge in the induction of neuropathic pain behaviour in rats. *Pain* 1991; **46**: 327–336.
9. Woolf CJ, Chong M. Pre-emptive analgesia—treating post-operative pain by preventing the establishment of central sensitization. *Anesthesia and Analgesia* 1993; **77**: 362–379.
10. Munglani R, Bond A, Smith G, Harrison S, Elliot PJ, Birch PJ, Hunt SP. Changes in neuronal markers in a mono-neuropathic rat model: relationship between Neuropeptide Y, pre-emptive drug treatment and long term mechanical hyperalgesia. *Pain* 1995 (in press).
11. Tolle TR, Schadrack J, Castro-Lopes JM, Zieglganberger W. Immediate early genes in nociception. In: Tolle TR, Schadrack J, Zieglgansberger W, eds. *Immediate Early Genes in the Central Nervous System*. Berlin: Springer, 1995; 51–77.
12. Tolle TR, Schadrack J, Castro-Lopez JM, Evan G, Roques BP, Zieglgansberger W. Effects of kelatorphan and morphine before and after noxious stimulation on immediate–early gene expression in rat spinal cord neurons. *Pain* 1994; **56**: 103–112.
13. Bach S, Noreng MF, Tjellen NU. Phantom limb pain in amputees during the first 12 months following limb amputation after preoperative lumbar epidural blockade. *Pain* 1988; **33**: 297–301.
14. Wall PD. The prevention of postoperative pain. *Pain* 1988; **33**: 289–290.
15. Fisher A, Meller Y. Continuous postoperative regional analgesia by nerve sheath block for amputation surgery—a pilot study. *Anesthesia and Analgesia* 1991; **72**: 300–303.
16. Jebeles J, Reilly J, Gutierrez J, Bradley E, Kissin I. The effect of pre-incisional infiltration of tonsils with bupivacaine on the pain following tonsillectomy under general anaesthesia. *Pain* 1991; **47**: 305–308.
17. McQuay HJ. Pre-emptive analgesia. *British Journal of Anaesthesia* 1992; **69**: 1–3.
18. Richmond C, Bromley L, Woolf C. Preoperative morphine pre-empts postoperative pain. *Lancet* 1993; **342**: 73–53.
19. Orntoft S, Longreen A, Moniche S, Dhal JB. A comparison of pre and postoperative infiltration with bupivacaine on pain after tonsillectomy. A pre-emptive effect? *Anaesthesia* 1994; 94, 151–154.
20. Rogers JEG, Fleming BG, Macintosh KC, Johnston B, Morgan-Hughes JO. Effect of timing of ketorolac administration on patient-controlled opioid use. *British Journal of Anaesthesia* 1995; **75**: 15–18.
21. Munglani R, Jones JG, Hunt S. Pre-emptive analgesia—Use of immediate early gene expression as markers of neuronal stimulation. *British Journal of Anaesthesia* 1993; **71**: 458.
22. Presley RW, Menetrey D, Levine JD, Basbaum AI. Systemic morphine suppresses noxious stimulus-evoked Fos protein-like immunoreactivity in the rat spinal cord. *Journal of Neuroscience* 1990; **10**: 323–335.
23. Abram S, Olson E. Systemic opioids do not suppress spinal sensitization after subcutaneous formalin in rats. *Anesthesiology* 1994; **80**: 1114–1119.
24. Coderre TJ, Vaccarino AL, Melzack R. Central nervous system plasticity in the tonic pain response to subcutaneous formalin injection. *Brain Research* 1990; **535**: 155–158.
25. Cadet R, Aigouy L, Woda A. Sustained hyperalgesia can be induced in the rat by a formalin injection and depends on the initial nociceptive inputs. *Neuroscience Letters* 1993; **156**: 43–46.
26. Dallel R, Raboisson P, Clavelou P, Saade M, Woda A. Evidence for a peripheral origin of the tonic nociceptive response to subcutaneous formalin. *Pain* 1995; **61**: 11–16.
27. Naranjo JR, Mellstrom B, Achaval M, SassoneCorsi P. Molecular pathways of pain: Fos/Jun-mediated activation of a noncanonical AP-1 site in the prodynorphin gene. *Neuron* 1991; **6**: 607–617.
28. Lucas J, Mellstrom B, Colado M, Naranjo J. Molecular mechanisms of pain: Serotonin1A receptor agonists trigger transactivation by c-fos of the prodynorphin gene in spinal cord neurons. *Neuron* 1993; **10**: 599–611.
29. Hunter J, Woodburn VL, Durieux C, Pettersson E, Poat J, Hughes J. *c-fos* antisense oligodeoxynucleotide increases formalin-induced nociception and regulates preprodynorhin expression. *Neuroscience* 1995; **65**: 485–492.
30. Munglani R, Christadoulou E, Smith G, Harrison S, Elliot PJ, Birch PJ, Hunt SP. Persistent changes in neuronal

markers in a mononeuropathic rat model despite resolution mechanical hyperalgesia. *Brain Research Association Abstracts* 1995; **12**: 76.

31. Munglani R, Hunt S. Spinal cord and chronic pain. In: Kaufman L, ed. *Anaesthesia Review*. Edinburgh: Churchill Livingstone, 1995 (in press).
32. Munglani R, Hunt S. Molecular biology of pain. *British Journal of Anaesthesia* 1995; **75**: 186–192.
33. Crile GW. The kinetic theory of shock and its prevention through anoci-association (shockless operation). *Lancet* 1913; **185**: 7–16.
34. Katz J. George Washington Crile, anoci-association, and pre-emptive analgesia. *Pain* 1993; **53**: 243–245.
35. Abraham WC, Mason SE, Demmer J, Williams JM, Richardson CL, Tate WP, Lawlor PA, Dragunow M. Correlations between immediate early gene induction and the persistence of long-term potentiation. *Neuroscience* 1993; **56**: 717–727.
36. Hokfelt T, Zhang X, Wiesenfeld-Hallin Z. Messenger plasticity in primary sensory neurons following axotomy and its functional implications. *Trends in Neurosciences* 1994; **17**: 22–30.
37. Dickenson AH. Recent advances in the physiology and pharmacology of pain: plasticity and its implications for clinical analgesia. *Journal of Psychopharmacology* 1991; **5**: 342–351.
38. Urban L, Thompson SWN, Dray A. Modulation of spinal excitability: cooperation between neurokinin and excitatory amino acids neurotransmitters. *Trends in Neurosciences* 1994; **17**: 432–438.
39. Coderre T, Katz J, Vaccarino A, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain* 1993; **52**: 259–285.
40. Meller ST, Gebhart GF. Nitric oxide (NO) and nociceptive processing in the spinal cord. *Pain* 1993; **52**: 127–136.
41. Wilcox GL. Excitatory neurotransmitters and pain. In: Bond MR, Charlton JE, Woolf, CJ, eds. *Proceedings of the VIth World Conference on Pain*. Amsterdam: Elsevier, 1991; 97–118.

British Journal of Anaesthesia 1996; **76**: 5–8

CLINICAL INVESTIGATIONS

Dobutamine increases oxygen consumption during constant flow cardiopulmonary bypass

W. Karzai, A. Lötte, M. Günnicker, U. M. Vorgrimler-Karzai and H.-J. Priebe

Summary

We have studied the effects of flow and dobutamine on systemic haemodynamic variables, oxygen delivery ($D\text{O}_2$) and oxygen consumption ($\dot{V}\text{O}_2$) in 20 patients during cardiopulmonary bypass (CPB) with mild hypothermia (34 °C). In a subgroup of seven patients, we also studied the effects on gastric microcirculatory blood flow (MCF) using laser Doppler flowmetry. During CPB, measurements were made before and after two interventions: the first consisted of increasing flow from 2.4 to 3.0 litre $\text{min}^{-1}\ \text{m}^{-2}$ for 10 min; the second consisted of an infusion of dobutamine at a rate of 6 $\mu\text{g kg}^{-1}\ \text{min}^{-1}$ for 10 min during constant flow CPB. There were no significant differences in $D\text{O}_2$, $\dot{V}\text{O}_2$ or haemodynamic variables between the two baseline measurements. The increase in flow raised $D\text{O}_2$ (27%, $P < 0.001$), mean arterial pressure ($P < 0.01$) and MCF ($P < 0.01$), but failed to increase $\dot{V}\text{O}_2$. In contrast, dobutamine infusion increased $\dot{V}\text{O}_2$ (11%, $P < 0.001$) during constant flow CPB without significant changes in $D\text{O}_2$, systemic haemodynamic variables or MCF. These results indicate that increases in $\dot{V}\text{O}_2$ during dobutamine may be flow-independent. (*Br. J. Anaesth.* 1996; **76**: 5–8)

Key words

Heart, dobutamine. Heart, cardiopulmonary bypass. Oxygen, consumption.

The synthetic catecholamine, dobutamine, is frequently used in critically ill patients to increase cardiac output and oxygen delivery ($D\text{O}_2$) [1, 2]. Normally, changes in cardiac output or $D\text{O}_2$ only minimally influence systemic oxygen consumption ($\dot{V}\text{O}_2$) [3]. However, in pathological states, $\dot{V}\text{O}_2$ is presumed to become delivery-dependent [3], possibly because of an increase in flow and $D\text{O}_2$ to less well perfused areas of the circulation. Dobutamine infusion has been used in critically ill patients, not only diagnostically to uncover delivery-dependent $\dot{V}\text{O}_2$, but also therapeutically to increase perfusion to less well perfused areas of the organism [1, 2, 4].

Several studies have reported an increase in metabolic rate during various catecholamine infusions [5–8]. These studies suggest that at least part of the increase in $\dot{V}\text{O}_2$ infusion may be explained by the calorigenic effect of the catecholamine, unrelated to increases in flow or $D\text{O}_2$. In healthy humans, dobutamine has been shown to increase $\dot{V}\text{O}_2$ [8, 9]. However, the increase in $\dot{V}\text{O}_2$ was accompanied by an increase in cardiac output, thus not conclusively demonstrating flow-independent increases in $\dot{V}\text{O}_2$. Accordingly, the aim of this study was to study the flow-independent effects of dobutamine on $\dot{V}\text{O}_2$ and contrast them with the effects of flow on $\dot{V}\text{O}_2$. This was done using cardiopulmonary bypass (CPB) which, as we and others have shown [10–13], provides a means of studying the flow-independent effects of various interventions during constant flow without compromising patient safety. As redistribution of blood flow to metabolically active but underperfused areas of the circulation may increase $\dot{V}\text{O}_2$, even in the presence of unchanged flow, in addition we studied the effects of flow and dobutamine on the gastric microcirculation to uncover possible redistribution of blood to this area of the circulation.

Patients and methods

We studied 20 patients requiring CPB during cardiac surgery. The Ethics Committee of Essen University approved the study and all patients gave informed consent.

All patients received flunitrazepam 2 mg approximately 1 h before arriving in the operating room. An arterial catheter and a flow-directed pulmonary artery catheter were inserted under local anaesthesia. General anaesthesia was induced with etomidate 0.15–0.30 mg kg^{-1}, and fentanyl 5–7 $\mu\text{g kg}^{-1}$, followed by pancuronium 0.1 mg kg^{-1} and was maintained with 0.4–0.6 vol % isoflurane and 50 % nitrous oxide in oxygen. During operation and before CPB, increments of fentanyl 0.25 mg, pancuronium 2 mg and flunitrazepam 0.2 mg were given as needed. Fentanyl 0.25 mg and pancuronium 4 mg were added to the prime, and 0.4 vol % isoflurane was maintained during CPB. Extracorporeal circulation was maintained using non-pulsatile pump flow (Stöckert, Munich, Germany) at a standard flow rate of 2.4 litre $\text{min}^{-1}\ \text{m}^{-2}$. Oxygenation was provided

---

Waheedullah Karzai*, md, Hans-Joachim Priebe, md, Department of Anaesthesiology, University Hospital of Freiburg, Freiburg, Germany. Anke Lötte, md, Michael Günnicker, md, Uta Maria Vorgrimler-Karzai, Department of Anaesthesiology, University Hospital of Essen, Essen, Germany.

Accepted for publication: August 10, 1995.

*Address for correspondence: Anaesthesiologische Universitaetsklinik, Hugstetterstr. 55, 79106 Freiburg, Germany.

by a Cobe CML membrane oxygenator (Laboratories GmbH, Heimstetten, Germany). An asanguineous prime containing 1000 ml of lactated Ringer's solution, 10% hydroxyethylstarch 500 ml, 20% mannitol 100 ml and 8.4% sodium bicarbonate 100 ml was used. Packed cell volume was maintained above 20%. Blood temperature was kept at 34 °C. Measurements were made after CPB was commenced, the aorta was cross-clamped, the heart was in hypothermic cardioplegic arrest, and rectal and nasopharyngeal temperatures were within 0.8 °C of each other.

In seven of the 20 patients, gastric microcirculatory blood flow was studied using laser Doppler flowmetry (LDF) (MBF 3D, Moors Instruments Ltd, Devon, England). The measurement probe (fibreoptic wire < 3 mm ϕ) was inserted through the lumen of a nasogastric tube. The correct position of the nasogastric tube was confirmed by auscultation and aspiration of gastric contents. The correct position of the probe was verified by observing typical pulse synchronous oscillations. LDF uses the size and amount of the frequency shift caused by the back-scattered laser beam to calculate microcirculatory blood flow (MBF) [14]. LDF has been used experimentally to measure intestinal mucosal blood flow and has been found to correlate with mucosal blood flow, as measured by standard techniques [15].

Initial measurements were made at a flow rate of 2.4 litre min^{-1} m^{-2} (baseline 1). Flow was then increased to 3.0 litre min^{-1} m^{-2} (intervention 1), and repeat measurements were made 10 min later. Flow was then returned to and maintained at 2.4 litre min^{-1} m^{-2}, and measurements were repeated 5 min later (baseline 2). Subsequently, at unchanged flow, dobutamine 6 µg kg^{-1} min^{-1} was started (intervention 2), and repeat measurements were made 10 min later. At each of these times, samples were obtained for blood-gas analysis, and electrolyte and blood glucose concentrations from sampling ports of the CPB cannulae, and haemodynamic variables were recorded. Samples for blood-gas analysis were analysed immediately at 37 °C. $D\text{O}_2$ and $\dot{V}\text{O}_2$ were calculated according to the Fick method.

A repeated measures analysis of variance was used to test for differences between times. Paired *t* tests, corrected for multiple comparisons (Bonferroni), were used to test for differences between each baseline and subsequent intervention, and between the two baseline values [16]. Statistical significance was based on *P* values less than 0.05. Results are presented as mean (SD). The statistical program used was SAS (SAS Institute Inc., Cary, NC, USA) on an Accel (486DX33) Notebook computer (Accel Computers, Rockville, MD, USA).

Results

Patient data are summarized in table 1.

The increase in CPB flow rate from 2.4 to 3.0 litre min^{-1} m^{-2} significantly increased $D\text{O}_2$, mean arterial pressure (MAP) and gastric MCF, and decreased oxygen extraction (table 2). $\dot{V}\text{O}_2$ did not change significantly. In contrast, dobutamine 6 µg kg^{-1} min^{-1} for 10 min increased $\dot{V}\text{O}_2$ and oxygen extraction but MBF remained unchanged (table 2). Plasma concentrations of glucose and potassium were not affected by the two interventions. There were no significant differences in rectal temperature during the procedure (table 3).

Table 1 Patient characteristics (mean (SD or range) or number). CABG = Coronary artery bypass grafting; ACE = angiotensin-converting enzyme

Age (yr)	65 (53–75)
Weight (kg)	70 (11)
Sex (M/F)	12/8
Operation	
CABG	16
Valve replacement	4
Preoperative medication	
β Blockers	—
Nitrates	13
ACE inhibitors	7
Calcium antagonist	8
Digitalis glycosides	4
Diuretics	4

Discussion

In this study, we found that dobutamine, in clinical doses, increased $\dot{V}\text{O}_2$. This increase occurred in the presence of unchanged global and regional gastric mucosal flow and $D\text{O}_2$.

This finding of an increase in $\dot{V}\text{O}_2$ during dobutamine is in agreement with previous studies. In healthy volunteers, dobutamine 5–10 µg kg^{-1} min^{-1} was found to increase energy expenditure or $\dot{V}\text{O}_2$ by 20–33% [8, 9]. However, in these studies cardiac output (flow) presumably or measurably increased, whereas in our study flow was controlled. The smaller increase in $\dot{V}\text{O}_2$ (11%) found in our study may have been caused by a lack of increase in myocardial oxygen consumption, a lack of increase in total body blood flow in response to dobutamine, a higher basal catecholamine concentration during CPB [17] or by hypothermia.

We cannot explain why dobutamine increased $\dot{V}\text{O}_2$ without changing global blood flow. Flow-independent increases in $\dot{V}\text{O}_2$ in response to catecholamines may be caused by direct effects on effector cells, indirect effects on humoral factors (insulin and glucagon) or redistribution of blood flow, resulting in increased perfusion of metabolically active tissues [18]. The effects of catecholamines on metabolism are frequently accompanied by an increase in glucose and a decrease in potassium concentration [18]. This did not occur in our study. Redistribution of flow to less well perfused regions of the circulation could have been responsible for the increase in $\dot{V}\text{O}_2$. However, whereas the increase in flow (i.e. first intervention) increased MBF to one area of the circulation but failed to increase $\dot{V}\text{O}_2$, dobutamine failed to increase gastric MBF. These findings would suggest that redistribution of blood flow is unlikely to be a major cause of the increase in $\dot{V}\text{O}_2$ with dobutamine. In contrast, in a previous study using a similar design, dopamine increased gastric MBF without increasing $\dot{V}\text{O}_2$ [13]. However, some of the observed differences between dobu-

Table 2 Haemodynamic variables, oxygen delivery and oxygen consumption during the two interventions (mean (SD)). $\dot{V}O_2$ = Oxygen consumption; DO_2 = oxygen delivery; O_2-Ext = oxygen extraction; MAP = mean arterial pressure; SVRI = systemic vascular resistance index; CVP = central venous pressure; and MCF = microcirculatory gastric blood flow expressed in arbitrary units. *** $P < 0.001$, †† $P < 0.01$ compared with preceding value

	Flow intervention		Dobutamine (6 μg kg^{-1} min^{-1})	
	Before	After	Before	After
Flow rate (1 litre min^{-1} m^{-2})	2.4	3.0	2.4	2.4
$\dot{V}O_2$ (ml min^{-1} m^{-2})	66 (14)	70 (12)	66 (12)	73 (13)***
DO_2 (ml min^{-1} m^{-2})	250 (40)	319 (47)***	261 (35)	269 (38)
O_2-Ext	0.27 (0.05)	0.22 (0.04)***	0.25 (0.05)	0.28 (0.06)***
MAP (kPa)	9.2 (1.5)	10.1 (2.3)††	9.3 (2.3)	9.7 (2.3)
SVRI (dyn s cm^{-5} m^{-2})	2180 (347)	1948 (432)	2173 (551)	2285 (533)
CVP (kPa)	0.4 (0.3)	0.7 (0.6)	0.6 (0.5)	0.6 (0.6)
MCF (u.) ($n = 7$)	107 (29)	196 (92)††	126 (65)	132 (58)

Table 3 Potassium and glucose concentrations, and rectal temperature during the two interventions (mean (SD))

	Flow intervention		Dobutamine (6 μg kg^{-1} min^{-1})	
	Before	After	Before	After
Flow rate (1 litre min^{-1} m^{-2})	2.4	3.0	2.4	2.4
Glucose (mmol $litre^{-1}$)	6.4 (1.1)	7.1 (1.2)	7.4 (1.4)	7.8 (1.4)
Potassium (mmol $litre^{-1}$)	4.1 (0.4)	4.1 (0.4)	4.1 (0.4)	4.2 (0.5)
Temperature (°C)	34.3 (0.8)	34.3 (0.6)	34.1 (0.7)	34.1 (0.8)

tamine and dopamine on gastric blood flow may be caused by different receptor activities of these catecholamines on regional and systemic vasculature.

Randomization of the sequence of interventions (i.e. flow variation and dobutamine infusion) might have been preferable. However, as there are no data on the clearance of dobutamine during hypothermia, we chose not to randomize the sequence of interventions. The similar values before flow intervention and before dobutamine infusion are evidence of the stability of this model and return to baseline conditions after flow intervention.

As neuromuscular block is known to decrease $\dot{V}O_2$ [19], a possible decrease in block during the study might have affected the changes in $\dot{V}O_2$. However, as hypothermic CPB has been shown to reduce requirements [20] and increase the duration of action of pancuronium [21], and as pancuronium 4 mg was added to the prime of the extracorporeal circuit, it is highly unlikely that a decrease in neuromuscular block occurred during the study.

Even acknowledging the limitations of this study (i.e. hypothermia and surgical procedure with humoral activation), our finding may have implications for the diagnostic and therapeutic uses of dobutamine. Dobutamine has been used diagnostically in critically ill patients to increase DO_2 and uncover delivery-dependent $\dot{V}O_2$ [4]. As we have observed that dobutamine increased $\dot{V}O_2$, independent of DO_2, this diagnostic test may be of limited value. Furthermore, dobutamine has been used therapeutically to increase DO_2 and achieve supranormal values of $\dot{V}O_2$ in haemodynamically stable but critically ill patients in the hope of possibly increasing survival [22]. Our findings suggest caution in using dobutamine for this purpose. Dobutamine may further increase $\dot{V}O_2$, independent of increases in DO_2 or cardiac output (flow), and thus unnecessarily increase heart work and $\dot{V}O_2$, and possibly endanger the patient. A recent study suggested that increasing $\dot{V}O_2$ with dobutamine to achieve supranormal values in critically ill patients may increase mortality [23].

Acknowledgements

This study was performed in the Department of Thoracic and Cardiovascular Surgery, University Hospital Essen. We acknowledge the support of Horst Schmidt, Josef Graban and Helmut Hees, Perfusionists, Department of Thoracic and Cardiovascular Surgery, and Susanne Spitzer, Regine Pohl and Beate Lehnen-Lutzke, Department of Anaesthesiology, University Hospital Essen, Essen, Germany.

References

1. Vincent J-L, Roman A, Backer de D, Kahn RJ. Oxygen uptake/supply dependency: Effects of short-term dobutamine infusion. *American Review of Respiratory and Critical Care Medicine* 1990; **142**: 2–8.
2. Vincent J-L, Roman A, Kahn RJ. Dobutamine administration in septic shock: Addition to a standard protocol. *Critical Care Medicine* 1990; **18**: 689–693.
3. Cain SM, Curtis SE. Experimental models of pathologic oxygen supply dependency. *Critical Care Medicine* 1991; **19**: 603–612.
4. de Backer D, Moraine J-J, Berre J, Kahn RJ, Vincent J-L. Effects of dobutamine on oxygen consumption in septic patients. *American Journal of Respiratory and Critical Care Medicine* 1994; **150**: 95–100.
5. Blaak EE, van Baak MA, Kempen KPG, Saris WHM. Role of alpha- and beta-adrenoreceptors in sympathetically mediated thermogenesis. *American Journal of Physiology* 1993; **264**: E11–E17.
6. Ruttimann Y, Chioléro R, Jéquier E, Breitenstein E, Schutz Y. Effects of dopamine on total oxygen consumption and oxygen delivery in healthy men. *American Journal of Physiology* 1989; **257**: E541–E546.
7. Abdul-Rasool IH, Chamberlain JH, Swan PC, Ward DS.

Cardiorespiratory and metabolic effects of dopamine and dobutamine infusions in dogs. *Critical Care Medicine* 1987; **15**: 1044–1050.

8. Bhatt S, Hutchinson R, Tomlinson B, Oh T, Mak M. Effects of dobutamine on oxygen supply and uptake in healthy volunteers. *British Journal of Anaesthesia* 1992; **69**: 298–303.
9. Green CJ, Frazer RS, Underhill S, Maycock P, Fairhurst JA, Campbell IT. Metabolic effects of dobutamine in normal man. *Clinical Science* 1992; **82**: 77–83.
10. Videcoq M, Desmonts J-M, Marty J, Hazebroucq J, Langlois J. Effects of droperidol on peripheral vasculature: Use of cardiopulmonary bypass as a study model. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 370–374.
11. Evans PJD, Ruygrok P, Seelye ER, Harris EA. Does sodium nitroprusside improve oxygenation during cardiopulmonary bypass? *British Journal of Anaesthesia* 1977; **49**: 799–803.
12. Karzai W, Günnicker M, Vorgrimler-Karzai U-M, Freund U, Zerkowski H-R. The effects of beta-adrenoreceptor blockade on oxygen consumption during cardiopulmonary bypass. *Anesthesia and Analgesia* 1994; **79**: 19–22.
13. Karzai W, Scharbert G, Günnicker M, Vorgrimler-Karzai U-M, Freund U, Doetsch N, Kox WJ. Dopamine increases gastric microcirculatory blood flow during constant flow cardiopulmonary bypass. *Clinical Intensive Care* 1994; **5** (Suppl.): 22.
14. Stern MD. In vivo evaluation of microcirculation by coherent light scattering. *Nature (London)* 1975; **254**: 56–58.
15. Ahn H, Lindhagen J, Nilsson GE, Salerud EG, Jodal M, Lundgren O. Evaluation of laser flowmetry in the assessment of intestinal blood flow in cat. *Gastroenterology* 1985; **88**: 951–957.
16. Ludbrook J. Repeated measurements and multiple comparisons in cardiovascular research. *Cardiovascular Research* 1994; **28**: 303–311.
17. Wallach R, Karp RB, Reves JG, Smith LR, James TN. Pathogenesis of paroxysmal hypertension developing during and after coronary bypass surgery: A study of hemodynamic and humoral factors. *American Journal of Cardiology* 1980; **46**: 559–565.
18. Macdonald IA, Bennet T, Fellows IW. Catecholamines and control of metabolism in man. *Clinical Science* 1985; **68**: 613–619.
19. Irish CL, Murkin JM, Cleland A, Macdonald JL, Mayer R. Neuromuscular blockade significantly decreases systemic oxygen consumption during hypothermic cardiopulmonary bypass. *Journal of Cardiothoracic and Vascular Anesthesia* 1991; **5**: 132–134.
20. D'Hollander AA, Duvaldestin P, Henzel D, Nevelsteen M, Bomblet JP. Variations in pancuronium requirement, plasma concentration, and urinary excretion induced by cardiopulmonary bypass with hypothermia. *Anesthesiology* 1983; **58**: 505–509.
21. Buzello W, Schluermann D, Schindler M, Spillner G. Hypothermic cardiopulmonary bypass and neuromuscular blockade by pancuronium and vecuronium. *Anesthesiology* 1985; **62**: 201–204.
22. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee T. Prospective trial of supernormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 1988; **94**: 1176–1186.
23. Hayes MA, Timmins AC, Yau EHS, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *New England Journal of Medicine* 1994; **330**: 1717–1722.

British Journal of Anaesthesia 1996; **76**: 9–12

Effects of sevoflurane and isoflurane on systemic vascular resistance: use of cardiopulmonary bypass as a study model

G. RÖDIG, C. KEYL, G. WIESNER, A. PHILIPP AND J. HOBBHAHN

Summary

We have examined the dose-related effects of sevoflurane and isoflurane on systemic vascular resistance (SVR) during cardiopulmonary bypass (CPB) in patients undergoing elective coronary artery surgery. Fifty-two patients were allocated randomly to one of six groups to receive 1.0, 2.0 or 3.0 vol% (inspiratory) sevoflurane or 0.6, 1.2 or 1.8 vol% isoflurane, or to a control group. During hypothermic (32–33 °C) non-pulsatile CPB, systemic vascular resistance index (SVRI) was recorded before administration of volatile anaesthetics and every 5 min for 20 min. Sevoflurane and isoflurane concentrations were measured next to the gas inlet port and at the gas outlet port of the oxygenator. Wash-in of sevoflurane occurred more rapidly than that of isoflurane, reaching a relatively steady state for both agents from the 10th to the 20th min. There was no significant change in SVRI in patients receiving 1.0 and 2.0 vol% sevoflurane, and 0.6 and 1.2 vol% isoflurane, compared with baseline values. However, 3 vol% sevoflurane decreased SVRI at 10, 15 and 20 min, and 1.8 vol% isoflurane decreased SVRI significantly at 15 and 20 min, whereas SVRI increased at 15 and 20 min in the control group. Thus during CPB, sevoflurane had similar vasodilator effects on SVRI as isoflurane. (*Br. J. Anaesth.* 1996; **76**: 9–12)

Key words

Heart, cardiopulmonary bypass. Anaesthetics volatile, isoflurane. Anaesthetics volatile, sevoflurane. Cardiovascular system, effects.

Studies comparing the cardiovascular effects of isoflurane with sevoflurane in surgical ASA I and II patients found similar changes in mean arterial pressure [1–4]. The decrease in arterial pressure caused by sevoflurane may result from depression of myocardial contractility and decreased peripheral vascular resistance [5]. As there are only few data available in volunteers focusing on the influence of sevoflurane on systemic vascular resistance (SVR) [6], we administered sevoflurane during cardiopulmonary bypass (CPB) and compared its effects with those of isoflurane. CPB is considered a useful model for studying the isolated effects of drugs on the systemic vasculature, as cardiac effects are excluded during aortic cross-clamping [7–13].

Patients and methods

After obtaining written informed consent, we studied 52 patients (35 male), median age 67 yr (range 36–80 yr), undergoing elective coronary artery surgery. The study was approved by the local Ethics Committee. Patients were excluded if they had a history of central nervous system disease, significant renal or hepatic impairment, peripheral vascular disease or an ejection fraction of < 50%.

Patients were premedicated with clorazepate 20–30 mg orally on the evening before surgery, and clorazepate 20 mg approximately 1 h before operation. All patients received their routine anti-anginal and antihypertensive medication up to and including the morning of surgery. Anaesthesia was induced with fentanyl 5 μg kg^{-1} i.v., followed by a sleep dose of etomidate. Neuromuscular block was produced with pancuronium 100 μg kg^{-1}. Anaesthesia was maintained before CPB with an infusion of propofol 5 mg kg^{-1} h^{-1}, supplemented with fentanyl bolus doses up to 20 μg kg^{-1} and pancuronium 50 μg kg^{-1}.

A standard CPB technique was used in all patients. Before aortic cannulation patients were anti-coagulated with heparin (375 u. kg^{-1}). The bypass circuit consisted of a capillary membrane oxygenator (Maxima/plus, Medtronic, Anaheim, CA, USA) and a roller pump (Stöckert Instruments, Munich, Germany), which was primed with a crystalloid solution. A hard-shell venous reservoir, open to air, was used, with an integral cardiotomy reservoir.

The 52 patients were allocated randomly to one of six groups of seven patients, or to a control group of 10 patients. After application of the aortic cross-clamp and administration of cold cardioplegic solution (Kardioplegische Perfusionslösung Fresenius, Bad Homburg, Germany), time was allowed to develop a stable level of perfusion pressure and mild hypothermia (arterial and bladder temperatures 32–33 °C). These variables remained constant for at least 10 min before initiating the test sequence. Baseline values were recorded at the end of the stabilization period. Thereafter, patients allocated to group 1 received 1.0 vol% sevoflurane, group 2, 0.6

GABRIELE RÖDIG, MD, CORNELIUS KEYL, MD, GUNTHER WIESNER, MD, ALOIS PHILIPP, JONNY HOBBHAHN, MD, University Hospital, Department of Anaesthesiology, Franz-Josef-Strauss-Allee 11, 93042 Regensburg, Germany. Accepted for publication: July 26, 1995.

Correspondence to G.R.

vol % isoflurane, group 3, 2.0 vol % sevoflurane, group 4, 1.2 vol % isoflurane, group 5, 3.0 vol % sevoflurane and group 6, 1.8 vol % isoflurane, the volatile anaesthetics being administered via a vaporizer inserted into the oxygenator gas supply line with a constant gas flow of 3 litre min^{-1}. Patients in the control group received no volatile anaesthetic or additional i.v. anaesthetic during the study. Anaesthetic gas concentrations were measured for both sevoflurane and isoflurane with a Datex multiple gas analysis monitor (Capnomac Ultima, Hoyer, Bremen, Germany) next to the gas inlet port of the oxygenator, and were adjusted continuously to "inspiratory" values. Gas concentrations of both agents were measured also at the gas outlet port of the oxygenator.

Non-pulsatile perfusion and alpha-stat acid–base management were used. Pump flows were 2.4 litre min^{-1} m^{-2} throughout the study. Packed cell volume was determined at the beginning and end of the test sequence. The time available for study at stable hypothermia was 20 min.

Systemic arterial pressures, measured via a femoral artery cannula, were monitored continuously throughout the procedure and, at the end of each 5-min period, recordings were made of mean arterial pressure (MAP). Systemic vascular resistance (SVR) was calculated from MAP (mm Hg) and pump flow rate, $\dot{Q}$ (litre min^{-1}) as: $SVR = (MAP/\dot{Q}) \times 80$ (dyn s cm^{-5}). Systemic vascular resistance index (SVRI) was equal to SVR × body surface area (BSA). Hypotension during CPB requiring intervention was defined as MAP < 35 mm Hg and hypertension as MAP > 90 mm Hg. When intervention became necessary patients were withdrawn from the study.

All data are presented as median (range). Differences between changes in SVRI from baseline values and time-dependent changes in the ratio of exhaust gas to inspired anaesthetic concentrations were tested using the Friedmann two-way analysis of variance followed by the Wilcoxon and Wilcox test for repeated measurements. $P < 0.05$ was considered significant.

Results

There were no significant differences between the groups in age, weight, body surface area or preoperative medication. The groups did not differ in intraoperative medications before the study.

Figure 1 shows the ratio of exhaust gas anaesthetic concentrations (*F*E) to inspired anaesthetic concentrations (*F*I) at times when SVRI was recorded. We present pooled data from groups 1, 3 and 5 (1, 2 and 3 vol % sevoflurane) and 2, 4 and 6 (0.6, 1.2 and 1.8 vol % isoflurane) to illustrate the pharmacokinetics during wash-in of both volatile anaesthetics, as there were no significant differences in *F*E/*F*I between 1, 2, 3 vol % sevoflurane or between the three isoflurane groups. *F*E/*F*I for sevoflurane increased more rapidly than for isoflurane, reaching a median equilibration after 20 min of 68 % (range 62–80 %) for sevoflurane and of 49 % (36–60 %) for isoflurane. *F*E/*F*I at 5 min was significantly different for both the sevoflurane and isoflurane curves compared with *F*E/*F*I ratios after 10, 15 and 20 min, whereas there was no change in *F*E/*F*I between the 10-, 15- and 20-min values for both drugs.

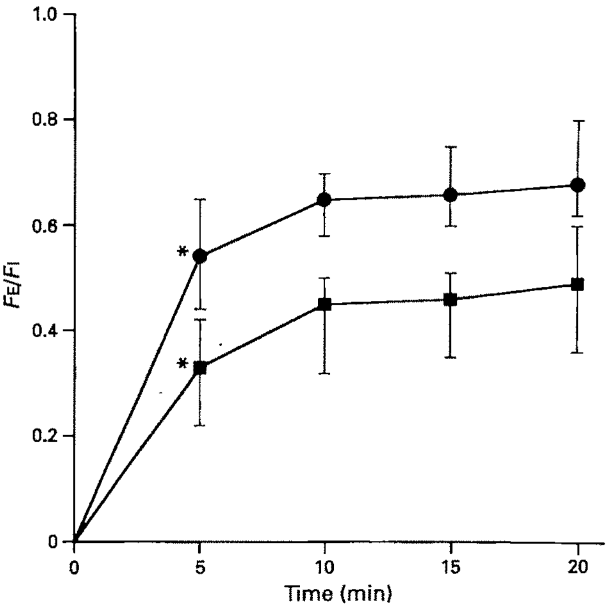


Figure 1 Ratio of exhaust gas concentrations (*F*E) to inspired anaesthetic concentrations (*F*I) (median, range) during washin of sevoflurane (●) and isoflurane (■). $*P < 0.05$ *vs* 10, 15 and 20 min.

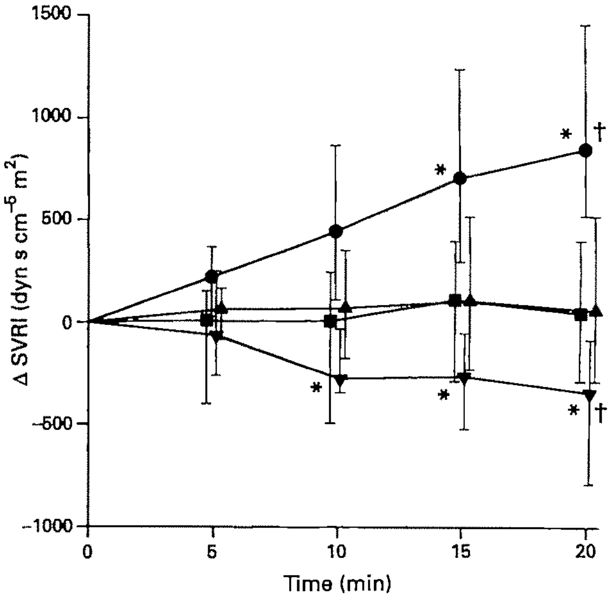


Figure 2 Changes in systemic vascular resistance index (SVRI) from baseline values (median, range) in 1.0 vol % (■), 2.0 vol % (▲) and 3.0 vol % (▼) sevoflurane treated and control (●) patients. $*P < 0.05$ *vs* 0 min; $\dagger P < 0.05$ *vs* 5 min.

Figure 2 presents the changes in SVRI from baseline values in those patients treated with sevoflurane and in the control group. There was no significant change in SVRI at any time in those patients receiving 1.0 and 2.0 vol % sevoflurane. In the 3.0 vol % sevoflurane group, significant changes in SVRI were observed at 10, 15 and 20 min compared with the baseline value, and at 20 min compared with the 5-min value.

In patients receiving 0.6 and 1.2 vol % isoflurane, there was no difference in SVRI with time (fig. 3),

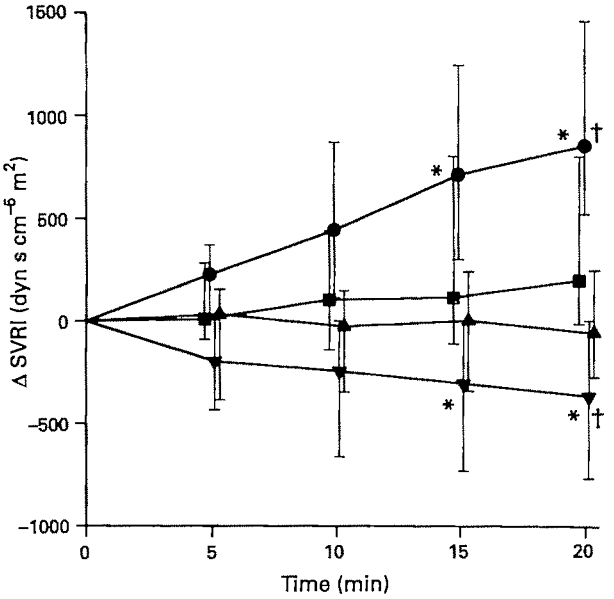


Figure 3 Changes in SVRI from baseline value (median, range) in 0.6 vol% (■), 1.2 vol% (▲) and 1.8 vol% (▼) isoflurane treated and control (●) patients. $*P < 0.05$ *vs* 0 min; $\dagger P < 0.05$ *vs* 5 min.

that is SVRI was maintained equally at baseline in these two groups. There were significant decreases in SVRI in the 1.8 vol% isoflurane group compared with baseline values at 15 and 20 min. The 20-min value also differed significantly from the 5-min value. In contrast, in the control group there was a significant increase in SVRI at 15 and 20 min compared with baseline values, and also at 20 min compared with the 5-min values. The change in SVRI, expressed as a percentage change from baseline values, at 15 min was −16% (median) for 3.0 vol% sevoflurane (range −3 to −22%) compared with −20% (0 to −35%) for 1.8 vol% isoflurane; at 20 min changes of −24% (−5 to −35%) for 3.0 vol% sevoflurane and of −24% (0 to −42%) for 1.8 vol% isoflurane were noted. The increase in SVRI in the control group, expressed as a percentage change from baseline, corresponded to an increase of 50% (+28 to +108%) at 15 min and to an increase of 66% (+49 to +127%) at 20 min.

Hypotension or hypertension requiring intervention occurred in none of the 42 patients treated with sevoflurane and isoflurane. However, two patients in the control group were excluded because of hypertension (MAP > 90 mm Hg). Packed cell volume did not change in any patient during the 20-min study.

Discussion

Volatile anaesthetics are known to induce hypotension because of effects on the central and autonomic nervous system, on the myocardium and because of a direct action on vascular smooth muscle. To exclude myocardial effects, we administered sevoflurane and isoflurane during CPB, as cardiac responses need not to be considered during aortic cross-clamping. This situation has been used as a model by others interested in the vasoactive properties of anaesthetic agents such as propofol [7,8], diazepam [9], thiopentone [10], etomidate [10], droperidol [11], isoflurane [12,13] or halothane [13].

We administered 1.0, 2.0 and 3.0 vol% "inspiratory" sevoflurane and 0.6, 1.2 and 1.8 vol% isoflurane over a 20-min period. Sevoflurane 2.0 vol% [14] and 1.2 vol% isoflurane correspond to approximately 1 MAC.

Wash-in of the volatile anaesthetics occurred in a cold phase with arterial blood and bladder temperatures maintained at 32–33 °C. Relative to isoflurane, *F*E/*F*I increased more rapidly with sevoflurane. The partition coefficient in undiluted normothermic blood is 0.65 for sevoflurane and 1.4 for isoflurane [14]. Similar differences may be assumed during hypothermic CPB because of the counterbalancing effects of haemodilution and hypothermia on blood-gas partition coefficients [15]. As observed by Nussmeier and colleagues [16], we found that wash-in of volatile anaesthetics occurred more slowly during CPB than would be expected from the pharmacokinetic data of drugs administered via the lungs in normothermic patients [17]. After an initial rapid increase there were no significant changes in *F*E/*F*I ratios from 10 to 20 min for both agents, indicating a relatively steady state.

We calculated SVRI from MAP, a fixed pump flow rate and body surface area. As venous drainage was adequate at all times, we assumed that central venous pressure was zero. The venous reservoir volume did not reflect changes in capacitance vessels as we used a venous reservoir with an integral cardiotomy reservoir.

We did not find significant changes in SVRI from baseline over the 20-min period with 1.0 and 2.0 vol% sevoflurane. The same time course in ΔSVRI, with no difference from baseline values over 20 min, was obtained when anaesthesia was maintained with 0.6 and 1.2 vol% isoflurane, whereas SVRI increased significantly compared with baseline at 15 and 20 min in the control group. Two patients in this group had to be withdrawn from the study as MAP exceeded 90 mm Hg. This increase in SVRI reflects the usual pattern of SVR increasing during hypothermic non-pulsatile CPB, which probably results from a marked stress response, as indicated by increases in adrenaline, noradrenaline [18,19] and arginine vasopressin [20]. Mediators such as thromboxane may also play a role [21].

Vasodilatation capacity was evident by the decrease in SVRI with higher concentrations of sevoflurane and isoflurane. Inspiratory concentrations of 3 vol% sevoflurane and 1.8 vol% isoflurane reduced SVRI significantly 10 min after commencing sevoflurane and after 15 and 20 min for both drugs compared with baseline values. The finding that SVRI and, thus, perfusion pressure decreased significantly during administration of 1.5 MAC of sevoflurane and isoflurane implies that both agents caused arteriolar vasodilatation.

Hence, we found that sevoflurane in low, medium and higher inspiratory concentrations had similar effects on SVRI as those of isoflurane. Our results are in accordance with the findings of Malan and colleagues [22] who showed that the changes in SVR were qualitatively similar to those of isoflurane.

Vasodilatation may be attributed to the direct relaxant actions on vascular smooth muscle [23, 24], reduction in sympathetic output [25] or reduction in the effectiveness of other stimuli on the vascular smooth muscle. The precise mechanisms cannot be identified in the complex clinical situation.

References

1. Navarro R, Weiskopf RB, Moore MA, Lockart S, Eger EI II, Koblin D, Lu G, Wilson C. Humans anesthetized with sevoflurane or isoflurane have similar arrhythmic response to epinephrine. *Anesthesiology* 1994; **80**: 545–549.
2. Frink EJ, Malan TP, Atlas M, Dominguez LM, DiNardo JA, Brown BR. Clinical comparison of sevoflurane and isoflurane in healthy patients. *Anesthesia and Analgesia* 1992; **74**: 241–245.
3. Quinn AC, Newman PJ, Hall GM, Grounds RM. Sevoflurane anaesthesia for major intra-abdominal surgery. *Anaesthesia* 1994; **49**: 567–571.
4. Smith I, Ding Y, White PF. Comparison of induction, maintainance, and recovery characteristics of sevoflurane–N_2O and propofol–sevoflurane–N_2O with propofol–isoflurane–N_2O anesthesia. *Anesthesia and Analgesia* 1992; **74**: 253–259.
5. Kikura M, Ikeda K. Comparison of effects of sevoflurane/nitrous oxide and enflurane/nitrous oxide on myocardial contractility in humans. *Anesthesiology* 1993; **79**: 235–243.
6. Malan TP, DiNardo JA, Isner RJ, Frink EJ, Goldberg M, Brown EA, Depa R. Cardiovascular effects of sevoflurane in volunteers. *Anesthesia and Analgesia* 1994; **78**: S262.
7. Pensado A, Molins N, Alvarez J. Effects of propofol on mean arterial pressure and systemic vasculare resistance during cardiopulmonary bypass. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 398–501.
8. Baraka A, Dabbous A, Siddik S, Bijani A. Action of propofol on resistance and capacitance vessels during cardiopulmonary bypass. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 545–547.
9. Jacka MJ, Johnson GD, Milne B. Diazepam's effect on systemic vascular resistance during cardiopulmonary bypass is not caused by its vehicle (alcohol–propylene glycol). *Journal of Cardiothoracic and Vascular Anesthesia* 1993; **7**: 28–29.
10. Boer F, Bovill JG, Ros P, van Ommen H. Effect of thiopentone, etomidate and propofol on systemic vascular resistance during cardiopulmonary bypass. *British Journal of Anaesthesia* 1991; **67**: 69–72.
11. Videcoq M, Desmonts J-M, Marty J, Hazebroucq J, Langlois J. Effects of droperidol on peripheral vasculature: use of cardiopulmonary bypass as a study model. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 370–374.
12. Alston RP, Tierney C, McLaren AD. Isoflurane and hypothermic cardiopulmonary bypass: vasodilation without metabolic effects. *Journal of Cardiothoracic and Vascular Anesthesia* 1992; **80**: 906–922.
13. Doherty F, Wilkinson PL, Robinson S. Enflurane reduces systemic pressure during cardiopulmonary bypass more effectively than halothane. *Anesthesiology* 1981; **55**: A40.
14. Eger EI II. New inhaled anesthetics. *Anesthesiology* 1994; **80**: 906–922.
15. Nussmeier NA, Moskowitz GJ, Weiskopf RB, Cohen NH, Fisher DM, Eger EI. In vitro anesthetic washin and washout via bubble oxygenators: Influence of anesthetic solubility and rates of carrier gas inflow and pump blood flow. *Anesthesia and Analgesia* 1988; **67**: 982–987.
16. Nussmeier NA, Lambert ML, Moskowitz BA, Cohen NH, Weiskopf RB, Fisher DM, Eger EI II. Washin and washout of isoflurane administered via bubble oxygenators during hypothermic cardiopulmonary bypass. *Anesthesiology* 1989; **71**: 519–525.
17. Yasuda N, Lockhart SH, Eger EI II, Weiskopf RB, Liu J, Taheri S, Peterson NA. Comparison of kinetics of sevoflurane and isoflurane in humans. *Anesthesia and Analgesia* 1991; **72**: 316–324.
18. Reves JG, Karp RB, Buttner EE, Tosone S, Smith LR, Samuelson PN, Kreusch GR, Oparil S. Neuronal and adrenomedullary catecholamine release in response to cardiopulmonary bypass in man. *Circulation* 1982; **1**: 49–55.
19. Lehot JJ, Villard J, Piriz H, Phlbin DM, Carry P-Y, Gauquelin G, Claustrat B, Sassolas G, Galliot J, Estanove S. Hemodynamic and hormonal responses to hypothermic and normothermic cardiopulmonary bypass. *Journal of Cardiothoracic and Vascular Anesthesia* 1992; **6**: 132–139.
20. Philbin DM, Levine FH, Kono K, Coggins CH, Moss J. Slater EE, Buckley M. Attenuation of the stress response to cardiopulmonary bypass by the addition of pulsatile flow. *Circulation* 1981; **64**: 808–812.
21. Watkins WD, Peterson MB, Kong DL, Kono K, Buckley MJ, Levine FH, Philbin DM. Thromboxane and prostacyclin changes during cardiopulmonary bypass with and without pulsatile flow. *Journal of Thoracic and Cardiovascular Surgery* 1982; **84**: 250–256.
22. Malan TP, Dinardo JA, Frink JR, Isner RJ, Brown EA. Cardiovascular effects of sevoflurane and isoflurane in volunteers. *Anesthesiology* 1994; **81**: A131.
23. Yoshida K, Okabe E. Selective impairment of endothelium-dependent relaxation by sevoflurane: oxygen free radicals participation. *Anesthesiology* 1992; **76**: 440–447.
24. Nakamura K, Terasako K, Toda H, Miyawaki I, Kakuyama M, Nishiwada M, Hatano Y, Mori K. Mechanisms of inhibition of endothelium-dependent relaxation by halothane, isoflurane, and sevoflurane. *Canadian Journal of Anaesthesia* 1994; **41**: 340–346.
25. Ebert TJ, Muzi M. Sympathetic hyperactivity during desflurane anesthesia in healthy volunteers. *Anesthesiology* 1993; **79**: 444–453.

British Journal of Anaesthesia 1996; **76**: 13–19

Cardiopulmonary bypass with modified fluid gelatin and heparin-coated circuits

P. G. M. JANSEN, H. TE VELTHUIS, W. R. WILDEVUUR, M. A. J. M. HUYBREGTS, E. R. BULDER, H. I. VAN DER SPOEL, A. STURK, L. EIJSMAN AND C. R. H. WILDEVUUR

Summary

We have assessed the efficacy of cardiopulmonary bypass (CPB) using normal colloid oncotic pressure (COP) in a randomized, controlled study of 20 patients undergoing elective coronary artery surgery using heparin-coated circuits. For CPB, we used either crystalloid priming 1650 ml ($n = 10$) or colloid priming 1650 ml (2.4% modified fluid gelatin, $n = 10$). While COP did not change during bypass in the colloid group, a decline was observed in the crystalloid group ($P = 0.005$). By the end of bypass, the decrease in COP compared with baseline (ΔCOP) was 8.5 (S.D. 1.1) mm Hg in the crystalloid group compared with 1.5 (2.1) mm Hg in the colloid group ($P = 0.0001$). ΔCOP correlated positively with fluid balance during bypass ($r^2 = 0.41$, $P = 0.002$). Similar increments in complement factors C3b/c and C4b/c, tumour necrosis factor-α and neutrophil elastase, but not endotoxins, were found in both groups as indicators of a systemic inflammatory response. A clinical performance score composed of fluid balance, postoperative duration of intubation and the difference between rectal temperature and skin temperature was more favourable in patients treated with colloid priming ($P = 0.03$). Median postoperative hospital stay was 7 (range 5–16) days in the crystalloid group compared with 5 (4–8) days in the colloid group ($P = 0.016$). Regression analysis indicated that CPB time, fluid balance during operation and postoperative $P\text{O}_2/F\text{I}_{\text{O}_2}$ ratio were independent factors that predicted postoperative hospital stay. From these preliminary results we conclude that in the absence of endotoxaemia, use of a normal COP during CPB with modified fluid gelatin in heparin-coated circuits resulted in an improved postoperative course an a reduction in hospital stay. (*Br. J. Anaesth.* 1996; **76**: 13–19)

Key words

Heart, cardiopulmonary bypass. Blood, colloid oncotic pressure.

In adult cardiac surgery, haemodilution with clear priming solutions has become established clinical practice. If crystalloids primarily are used in the circuit priming, a sudden decrease in serum colloid oncotic pressure (COP) occurs after beginning cardiopulmonary bypass (CPB) [1, 2]. This leads to extravasation of fluids, with oedema formation and weight gain [3, 4]. Colloid-containing priming solutions are advocated to prevent the initial decrease in COP at the beginning of CPB. However, studies comparing crystalloid with colloid priming solutions were carried out with large priming volumes and failed to achieve a normal COP during CPB. The marginal clinical benefits observed fostered the controversy regarding the optimal prime composition [5–7].

The systemic inflammatory response that is characteristically observed after CPB may also contribute to increased microvascular permeability and hence a fluid shift towards the interstitial space. Exposure of blood to the artificial surfaces of the extracorporeal circuit activates host defence mechanisms [8, 9], while splanchnic hypoperfusion during CPB has been associated with intestine-derived endotoxin migration into the circulation [10]. Both phenomena result in release of inflammatory mediators and therefore also alter endothelial integrity.

Recently, several clinical studies reported that there was less complement activation products and, subsequently, a smaller systemic inflammatory response when heparin-coated circuits were used for CPB [11–13]. The present study was conducted to investigate if in patients treated with low-prime heparin-coated circuits, use of a normal COP by colloid priming elicits further benefits on the systemic inflammatory response, postoperative clinical performance and hospital stay.

Patients and methods

We studied 20 patients undergoing first-time coronary artery surgery. Study entry criteria coincided with the 80 % central range of the elective first-time coronary artery bypass grafting population at the

---

PIET G. M. JANSEN, MD, PHD, HENK TE VELTHUIS, PHD, WALTER R. WILDEVUUR, CCP, MARINUS A. J. M. HUYBREGTS, MD, LEÓN EIJSMAN, MD, PHD, CHARLES R. H. WILDEVUUR, MD, PHD (Center for Cardiopulmonary Surgery Amsterdam, Department of Cardiac Surgery); EISSO R. BULDER, MD (Department of Anesthesiology); HANS I. VAN DER SPOEL, MD (Department of Surgical Intensive Care); Free University Hospital, PO Box 7057, 1007 MB Amsterdam, the Netherlands. AUGUESTE STURK, PHD, Department of Clinical Chemistry, University Hospital, PO Box 9600, 2300 RC Leiden, the Netherlands. Accepted for publication: August 7, 1995.

Correspondence to P. G. M. J.

study hospital: age 45–75 yr and preoperative left ventricular end-diastolic pressure 10–35 mm Hg. Patients receiving acetylsalicylic acid in the 3 days before operation, those with preoperative coagulopathy or impaired organ function other than myocardial ischaemia and those receiving anti-inflammatory drugs were excluded. The patients were allocated randomly to one of two groups: 10 patients with crystalloid prime and no infusion of colloids during CPB (crystalloid group) and 10 patients with colloid-containing prime and infusion of colloids during CPB (colloid group). Except for the perfusionists, the clinical team was blinded to the randomization. Written informed consent was obtained from each patient and the study was approved by the Medical Ethics Committee of the Free University Hospital.

CHOICE OF COLLOID

In the study hospital, modified fluid gelatin (MFG, Gelofusine, NPBI BV, Emmer-Compascuum, Netherlands) is used as standard plasma substitute. Modified fluid gelatin (MFG) is prepared by alkaline hydrolysis and succinylation of bovine bone collagen. The weight average molecular weight of MFG is 35000 Da and the number average molecular weight is 22600 Da. Gelatin molecules are excreted mainly by glomerular filtration. The volume effect of MFG lasts 3–4 h, whereas its overall survival in blood is 168 h. Significant anaphylactic reactions to MFG occur in 1:6000 to 1:13000 u. administered, a ratio similar to other colloids [14]. MFG is presented as a 500-ml isotonic 4% solution and exerts a COP of 56 mm Hg to a 10000 Da membrane (Onkometer BMT 921, BMT Messtechnik GmBH, Berlin, Germany).

ANAESTHESIA AND CARDIOPULMONARY BYPASS

On the morning of surgery, patients received their usual early morning dose of antianginal medication and lorazepam 5 mg. Anaesthesia was induced with sufentanil 3 μg kg^{-1} i.v., pancuronium 0.1 mg kg^{-1} i.v. and midazolam 0.1 mg kg^{-1} i.v., and maintained with supplementary doses of these drugs. Cefuroxime 1.5 g was given i.v. for infection prophylaxis. After tracheal intubation, the lungs were ventilated to normocapnia using an oxygen–air mixture. Radial artery and thermodilution pulmonary artery catheters were inserted for haemodynamic measurements and obtaining blood samples. Fluid infusion before CPB consisted of MFG (500 ml maximum) and 0.9% NaCl (500 ml maximum).

The extracorporeal circulation system consisted of a soft-shell venous reservoir, roller pump, membrane oxygenator (Univox, Baxter Healthcare Corp, Irvine, CA, USA), arterial line filter, cardiotomy reservoir and polyvinyl tubing system. All parts of the extracorporeal circuit were treated with surface-bounded heparin (Duraflo II, Baxter). In all cases, the extracorporeal circuit was primed with 1650 ml. The prime solution in the crystalloid group contained lactated Ringer's solution 1500 ml, 20% mannitol 100 ml, 8.4% sodium bicarbonate 50 ml and heparin 5000 IE. The prime solution in the colloid group contained MFG 1000 ml, lactated Ringer's solution 500 ml, 20% mannitol 100 ml, 8.4% sodium bicarbonate 50 ml and heparin 5000 IE. In this prime composition, COP is 32 mm Hg and oncotic pressures were expected to be in the normal range (20–25 mm Hg in whole blood) after mixture of the prime with the patient's blood.

To perform sub-total CPB, a standard cannulation technique was used with cannulae placed in the ascending aorta and in the right atrium (two-stage venous cannula). After systemic heparinization (300 IE kg^{-1}), CPB was commenced, provided that the activated clotting time was more than 400 s. The left ventricle was vented via the aortic root. Blood from the pericardial cavity was collected in a cardiotomy reservoir and returned to the patient. Packed cell volume (PCV) during CPB was maintained at 22–24%; if possible, autologous blood was taken from the patient via the venous cannula just before the onset of extracorporeal circulation. Non-pulsatile flow rate was maintained at 2.2–2.4 litre min^{-1} m^{-2} and patients were cooled to 29–30 °C nasopharyngeal temperature. Mean arterial pressure during CPB was maintained at 50–80 mm Hg and if pressure declined to less than 50 mm Hg, flow rate was increased and vasoactive drugs were given. After aortic cross-clamping, all patients received crystalloid cardioplegia for myocardial protection (800–1000 ml, potassium 16 mmol litre^{-1}, 4 °C). Distal anastomoses of the grafts were placed during aortic cross-clamping, while proximal anastomoses were constructed after aortic cross-clamp release and recommencement of mechanical ventilation. Acid–base balance was managed following the alpha-stat concept. Patients were weaned from CPB using inotropic support if necessary. After termination of CPB, heparin was neutralized using an equivalent dose of protamine sulphate 3 mg kg^{-1}. Autologous blood and residual volume from the extracorporeal circuit were infused as first-choice fluid administration. Guided by low filling pressures, MFG and 0.9% NaCl were infused additionally.

POSTOPERATIVE CARE

After operation, all patients were transported to the intensive care unit (ICU), where they were treated according to a standard regimen. Haemodynamic units were: heart rate 70–80 beat min^{-1}, mean arterial pressure 65–80 mm Hg, pulmonary artery wedge pressure 8–12 mm Hg and cardiac index > 2.5 litre min^{-1} m^{-2}. Inotropic support was guided by the individual status of the patient. Fluid balance, rectal temperature and peripheral temperatures were recorded every hour. The peripheral circulation was considered to be adequate if the difference between rectal temperature and peripheral skin temperature (ΔT, measured on the back of the foot) was less than 5 °C. Patients were ventilated to normocapnia and an arterial oxygen tension > 11 kPa with continuous positive pressure breathing, and positive end-expiratory pressure of 5 cm H_2O. Extubation was permitted if the following criteria were met: (i) an awake and co-operative patient with a spontaneous ventilatory frequency of 10–20 bpm, (ii) positive pressure support ⩽ 5 cm H_2O, (iii) arterial oxygen tension > 11 kPa and (iv) inspired oxygen fraction ⩽ 40%. The minimal required postoperative intubation time, that is the moment that all four criteria were fulfilled, was recorded, independent of the medical decision to extubate the trachea at that time. Basic i.v. fluid administration consisted of 0.9% NaCl. MFG 4% and 20% human albumin (CLB, Amsterdam, Netherlands) were infused if COP was less than 15 mm Hg. Red packed cells were transfused if PCV was less than 26%. Blood loss and blood requirements were recorded until 18 h after operation.

BLOOD SAMPLING AND INFLAMMATORY MEDIATORS

All blood samples are obtained from the radial artery catheter or the arterial site of the extracorporeal circulation circuit. PCV, leucocyte counts and platelet counts were determined at all sample moments. Concentrations are not corrected for dilution.

Colloid oncotic pressure

Blood (1 ml) anticoagulated with ethylenedinitrotetra-acetate was used to measure whole blood COP. Samples were taken at the following times: 5 min before the start of CPB, 5 min, 20 min and 45 min after the start of CPB, at the end of CPB, and 1, 4 and 18 h after operation.

Endotoxin

Under pyrogen-free conditions, blood 6 ml was collected in heparin-anticoagulated tubes (Monovette, Sarstedt, Nümbrecht, Germany) and immersed immediately in crushed ice. After preparation of platelet-rich plasma, samples were stored at −70 °C in polystyrene tubes (Falcon 2063, Oxnard, CA, USA). Endotoxin concentrations were estimated using an optimized assay based on lipopolysaccharide-dependent activation of limulus amoebocyte lysate (LAL) and subsequent chromogenic measurement of activated LAL (Coatest Endotoxin, Kabi-Chromogenix, Molndal, Sweden). The LAL material contained in this batch of Coatest endotoxin kits is insensitive to LAL-reactive material, for example β-glucan, and therefore produces specific endotoxin data [15, 16]. The endotoxin concentration is presented as endotoxin units per millilitre of platelet-rich plasma (EU ml^{-1}), with 0.012 u. of endotoxin corresponding to 1 pg of endotoxin. The assay has a laboratory detection limit of 0.036 EU ml^{-1} and a clinical lower decision limit for endotoxaemia of 0.06 EU ml^{-1}. Blood samples were obtained before induction of anaesthesia (baseline), 10 min after the start of CPB, after cessation of CPB, and 1 and 18 h after arrival in the ICU. A sample was also obtained from the prime solution of the extracorporeal circuit just before connecting it to the patient.

Complement activation

Blood (2 ml) was collected in tubes and anticoagulated with ethylenedinitrotetra-acetate and immersed immediately in crushed ice. After preparation of platelet-poor plasma, samples were stored at −70 °C. C3b/c (C3b, iC3b and C3c) was measured using anti-C3-9 as capture antibody, which binds to C3b/c and also iC3. C4b/c (C4b, iC4b and C4c) was measured using anti-C4-1 as capture antibody, which binds to C4b/c and its degradation products C4b, iC4b and C4c. Blood samples were obtained before induction of anaesthesia, 20 min after the start of CPB, at the end of CPB, 20 min after protamine infusion and 4 h after arrival in the ICU.

Tumour necrosis factor-α (TNFα) and neutrophil elastase

Blood (2 ml) was collected in tubes containing citrate and immersed immediately in crushed ice. After preparation of platelet-poor plasma, its volume was divided in half, placed in two separate tubes and stored at −70 °C. Concentrations of TNFα were determined using an immunoradiometric assay (TNFα IRMA, Medgenix, Brussels, Belgium), with a detection limit of 5 ng $litre^{-1}$. Concentrations of neutrophil elastase were determined using an activating immunization method (Merck Diagnostica, Darmstadt, Germany) with an automated homogenous enzyme immunoassay (Hitachi 717 selective analyzer, Boehringer, Mannheim, Germany). Blood samples were obtained before induction of anaesthesia, after cessation of CPB, and 1, 4 and 18 h after arrival in the ICU.

ENDPOINTS OF THE STUDY

Fluid balance was calculated separately during CPB, at the operating room and during the first 18 h after operation. Volume of administered fluids, urine output, blood loss in surgical sponges and suction traps, and mediastinal and chest tube drainage were recorded. Insensible fluid losses were assumed equal among the groups and therefore were not included in the fluid balance.

To estimate the inflammatory response to CPB, a score based on face validity was used. Face validity refers to qualitative attributes of a score or index that are appraised with judgements of experts involved in patient treatment [17, 18]. This "clinical performance score" is composed of the sum of (i) the total fluid balance until 18 h after operation (measured during surgery and every hour at the ICU), (ii) mean ΔT during the first 18 h in the ICU (measured every 2 h) and (iii) time of fulfilment of extubation criteria divided by 4. In this way, all components of the score have a comparable range and therefore a comparable weight in the score. A higher score indicates a more pronounced inflammatory response.

The number of days in the cardiac surgical unit (ICU included) from surgery until transfer to the referring cardiologist was recorded. Criteria for transfer were: fully co-operative and mobile patient, walking stairs, devoid of chest tubes, without extra oxygen without pulmonary oedema on chest x-ray, signs of infection or arrhythmia in the last 24 h.

DATA ANALYSIS

Data were stored and analysed using standard computer software (Statview 4.02, Abacus concepts, Berkeley, CA). Inter-group comparisons were assessed with *t* tests, Mann–Whitney *U* test and Fisher's exact test. To analyse changes within each group, one factor analysis of variance (ANOVA) for repeated measures was applied, supplemented with the Scheffé *post hoc* test. The distribution of biochemical data displayed considerable skewness and underwent log transformation before ANOVA was performed. Regression analysis was performed if appropriate. A two-tailed $P < 0.05$ was considered to be statistically significant. Values are presented as mean (SD), unless mentioned otherwise.

Results

Patient and surgical data in the study groups are shown in table 1. No complications occurred. All patients survived and all but one were discharged from the ICU on the first postoperative day.

In the crystalloid group, COP during CPB was lower compared with levels before and after CPB (fig. 1, $P < 0.01$). In the colloid group, COP remained virtually unchanged during the study. Significant differences in COP between groups occurred at all times during CPB. At the end of CPB, the decrease in COP compared with baseline (ΔCOP) was 8.5 (SD 1.5) mm Hg in the crystalloid group compared with 1.5 (2.9) mm Hg in the colloid group ($P = 0.0001$). There was a positive correlation between ΔCOP and fluid balance during bypass ($r^2 = 0.41$, $P = 0.002$). Patients in the crystalloid group required more additional fluid during CPB compared with patients in the colloid group (table 2). Fluid balance during CPB and during surgery was more positive in the crystalloid group. There were no inter-group differences in PCV, white blood cell count and platelet count, or in diuresis, blood loss and number of units of blood transfused. In the total study population, MFG 4.4 litre (range 2–6.5 litre) was administered per patient over 24 h. There were no correlations between units of MFG and blood loss ($r^2 = 0.03$) or between units of MFG and blood transfusion ($r^2 = 0.01$). Respiratory function, as measured by $P\text{O}_2/F\text{I}_{\text{O}_2}$ ratio, did not differ between groups (table 2).

Table 1 Patient characteristics and surgical data (mean (SD or range) or number). There were no significant differences between the groups. BSA = Body surface area, CPB = cardiopulmonary bypass time, LIMA = left internal mammary artery, LVEDP = left ventricular end-diastolic pressure

	Crystalloid prime	Colloid prime
Age (yr)	63 (63–75)	65 (65–73)
Sex (M/F)	9/1	9/1
BSA (m^2)	1.93 (0.15)	1.97 (0.19)
LVEDP (mm Hg)	15 (4)	15 (4)
Predonation (y/n)	6/4	7/3
CPB (min)	110 (31)	115 (42)
Anastomoses	4 (3–6)	4 (3–7)
LIMA (y/n)	7/3	5/5

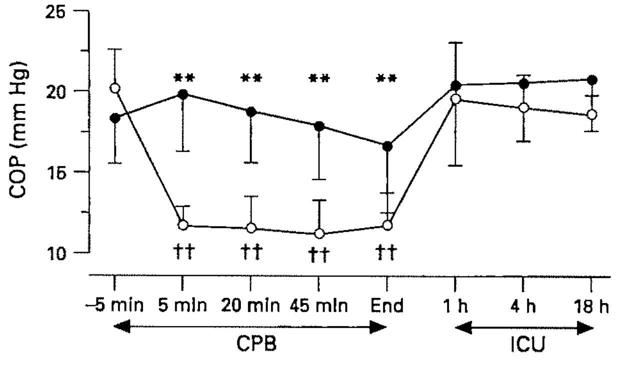


Figure 1 Colloid oncotic pressure (COP) during cardiopulmonary bypass (CPB) and in the intensive care unit (ICU) in patients treated with crystalloid prime (○) or colloid prime (●). $^{**}P < 0.01$ between groups; $^{\dagger\dagger}P < 0.01$ compared with baseline (–5 min CPB).

There were no differences in concentrations of inflammatory mediators between the groups (fig. 2). Throughout the study, endotoxin concentrations were near the limit of detection. C3b/c increased during CPB and after protamine infusion, followed by a decrease after 4 h in the ICU to levels that did not differ from baseline. C4b/c did not increase in each group during CPB or after protamine infusion. TNFα release exhibited a similar pattern in both groups, with increases during CPB and further increases to peak levels at 1 h in the ICU. Thereafter, TNFα concentrations decreased to levels that were not different from baseline. Positive correlations were found between TNFα at 4 h in the ICU and volume of fluid administration in the ICU ($r^2 = 0.32$, $P = 0.02$). Neutrophil elastase increased during CPB and levels after 18 h in the ICU were still higher compared with baseline.

There were no inter-group differences in mean arterial pressure, central venous pressure, pulmonary capillary wedge pressure, cardiac index (fig. 3), vascular resistance and vasoactive medication.

The clinical performance score and its components are depicted in table 3. A lower score was present in the colloid compared with the crystalloid group, whereas the individual components did not differ between groups. In each group, nine patients were transported to their referring hospital and one patient was discharged home (fig. 4). Median postoperative hospital stay for the referred patients was 7 (range 5–16) days in the crystalloid group and 5 (4–8) days in the colloid group ($P = 0.016$, Mann–Whitney test). A positive correlation was found between clinical performance score and postoperative hospital stay ($r^2 = 0.64$, $P = 0.0001$). To identify variables that influenced hospital stay, forward stepwise regression analysis was performed with the following independent variables: study category, sex, age, body surface area, duration of CPB and of aortic cross-clamping, ΔCOP, fluid balance, blood loss, mean ΔT, relative change in postoperative $P\text{O}_2/F\text{I}_{\text{O}_2}$ ratio and intubation time.

Table 2 Fluid balance (mean (SD) litre). Units presented as median (range). CPB = During cardiopulmonary bypass, ICU = in the intensive care unit, OR = in the operating room

	Crystalloid prime	Colloid prime	*P*
CPB			
Fluid in	3.9 (1.4)	2.5 (0.8)	0.01
Balance	2.7 (1.1)	1.1 (0.6)	< 0.001
OR			
Fluid in	7.2 (1.9)	5.3 (1.6)	0.03
Diuresis	1.8 (1.8)	1.5 (0.7)	ns
Blood loss	0.9 (0.3)	0.8 (0.8)	ns
Balance	4.5 (1.5)	3.0 (1.1)	0.03
ICU			
Fluid in	7.8 (2.2)	6.9 (1.5)	ns
Diuresis	5.3 (1.1)	4.7 (1.0)	ns
Blood loss	0.9 (0.3)	0.8 (0.3)	ns
Balance	1.7 (1.8)	1.5 (1.4)	ns
Donor blood (y/n)	9:1	7:3	ns
Units donor blood	2.5 (0–4)	1 (0–3)	ns
Units colloids	8 (4–12)	10 (6–13)	ns
Po_2/Fi_{O_2} before CPB	474 (210)	443 (323)	ns
Po_2/Fi_{O_2} after CPB	293 (115)	300 (99)	ns
% From baseline	72 (32)	82 (34)	ns
Po_2/Fi_{O_2} arrival ICU	292 (120)	300 (109)	ns
% From baseline	73 (39)	79 (25)	ns

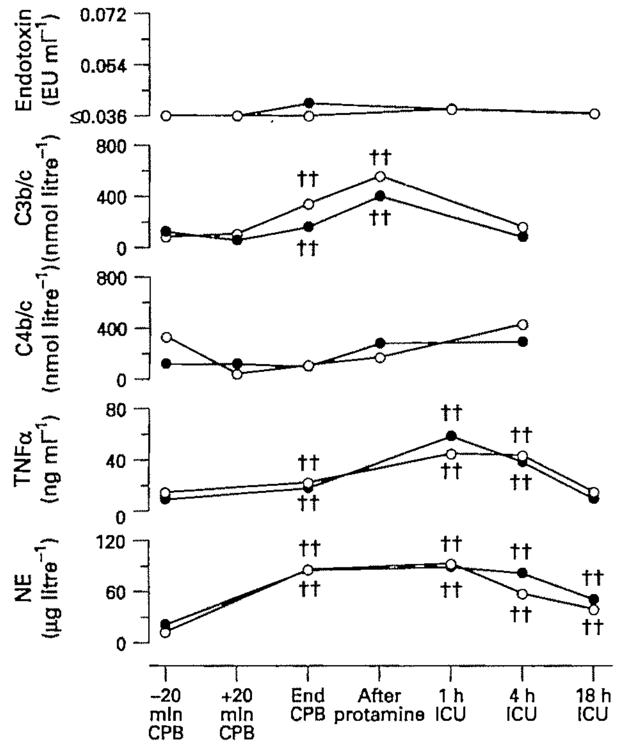


Figure 2 Median values of inflammatory mediators during cardiopulmonary bypass (CPB) and in the intensive care unit (ICU) in patients treated with crystalloid prime (○) or colloid prime (●). No significant differences were observed between groups. ††$P < 0.01$ compared with baseline (−5 min CPB). TNFα = Tumour necrosis factor-α, NE = neutrophil elastase.

The analysis yielded a regression model with three predictor variables: hospital stay = 2.37 + 0.01 × (CPB time) + 1.60 × (fluid balance at the end of the operation) − 3.28 × (Po_2/Fi_{O_2}), $r^2 = 0.87$, $P < 0.001$ (standard error of CPB time, 0.007, standard error of fluid balance, 0.18, standard error of Po_2/Fi_{O_2} ratio 0.002).

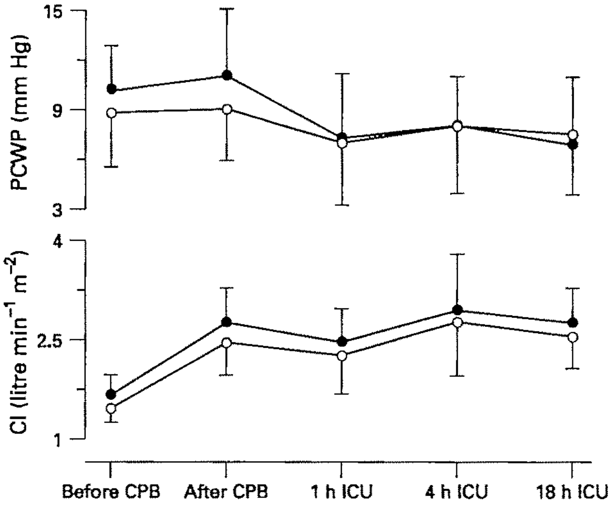


Figure 3 Pulmonary capillary wedge pressure (PCWP) and cardiac index (CI) before and after cardiopulmonary bypass (CPB) and in the intensive care unit (ICU) in patients treated with crystalloid prime (○) or colloid prime (●). No significant differences were observed between the groups. In both groups, CI after CPB and in the ICU was significantly higher compared with baseline.

Discussion

We have demonstrated that maintaining a normal COP during CPB can be established by adding MFG to the priming solution of a heparin-coated extracorporeal circuit with a small prime volume. The clinical benefits of a normal COP were reduced fluid administration, improved postoperative patient recovery and a shortened postoperative hospital stay.

Normal COP during CPB was achieved using a 2.4% MFG solution. This solution exerts a COP of 32 mm Hg, which is apparently sufficient to counteract the sudden haemodilution at the start of CPB and the cardioplegic solutions infused during aortic cross-clamping. The decline in COP at the onset of

Table 3 Clinical performance score = (i)+(ii)/4+(iii). Mean ΔT = Mean difference between rectal and peripheral skin temperature in the ICU, measured every 2 h until 18 h after operation. Values are mean (SD)

	Crystalloid prime	Colloid prime	P
(i) Fluid balance (litre)	5.6 (2.5)	3.8 (1.5)	ns
(ii) Extubation criteria (h)	21.9 (9.5)	18.7 (3.6)	ns
(iii) Mean ΔT (°C)	6.2 (1.5)	4.9 (2.3)	ns
Clinical performance score	17.3 (4.8)	13.3 (2.4)	0.03

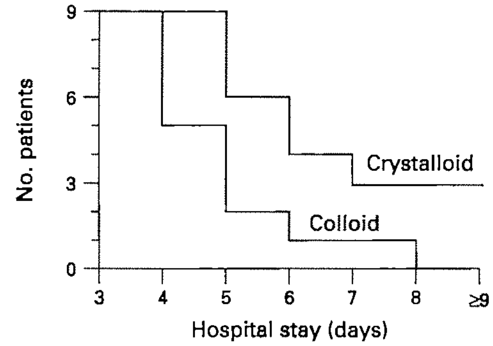


Figure 4 Patients treated with crystalloid prime had a longer postoperative hospital stay than those treated with colloid prime ($P < 0.02$).

CPB occurring with crystalloid primes induces fluid shifts across the capillaries [19]. To offset the low COP, extravascular stored albumin is transferred into the intravascular compartment in exchange for fluid shift towards the interstitial space [3]. Intravascular pressures are maintained within the normal range, but as observed in the crystalloid group, at the expense of a large amount of additional fluid administration during CPB.

The undetectable or low endotoxin concentrations found in this study may indicate that the intestinal microcirculation during and after cardiac surgery is not affected. Previously, we have reported endotoxaemia during CPB [20]. The initial vasoconstriction and duration of the low COP haemodilution were assigned as factors that determined the levels of endotoxin by the end of CPB. These findings prompted the clinical team to adjust the pre-CPB filling status of the patient, to modify the circuit by means of reduction in priming volume (from 2350 ml to 1650 ml) and to maintain an adequate arterial pressure during CPB. In this study with heparin-coated circuits, the inflammatory response was reduced. In these circumstances, COP maybe of secondary importance with regard to the intestinal microcirculation and endotoxin migration from the intestine into the circulation. In contrast, low COP during CPB, through its effects on fluid shifts, is likely to be a major contributory factor to intestinal ischaemia when capillary leakage occurs in association with an increased systemic inflammatory response.

The inhibitory effect of heparin coating on complement activation has been reported frequently [11–13]. As a sequel to reduced complement activation, there are decreased concentrations of neutrophil release products such as elastase, myeloperoxidase and lactoferrin [21]. In the present study, the pattern of complement activation was similar in both groups. Activation of the classic pathway, as represented by C4b/c, was not observed, either during CPB or after infusion of protamine [22]. Our findings emphasized that with the small prime volume heparin-coated circuits, in the absence of detectable endotoxins, activation of the alternative route of the complement cascade still occurred. The use of perfusion with normal COP apparently has no influence on activation of the complement cascade.

Sustained fluid administration was required in the postoperative phase in the crystalloid group and also in the colloid group, while no inter-group differences in COP or fluid balance were observed after operation. The reason for the rapid restoration of COP in the crystalloid group was probably that in both groups MFG was infused during sternal closure and in the ICU (table 2). In circumstances of profound haemodilution while on CPB, fluid administration is guided by sudden changes in COP. In the postoperative phase, when COP has returned to normal values, capillary leakage related to release of inflammatory mediators might determine the need for extra fluid infusion. This was confirmed by the, albeit weak, correlation between postoperative TNF concentrations and fluid administration during ICU stay. As shown in table 2, the contribution to the total fluid balance in both groups was higher during surgery than during ICU stay. The average stay in the operating room was approximately 4 h, while measurements in the ICU were spread over 18 h. The fluid shifts initiated by oncotic imbalance are likely to outweigh the contribution to interstitial fluid accumulation related to the inflammatory response.

In both groups, large amounts of MFG were administered. Few data are available on the efficacy of the recently available modified gelatins [23, 24]. In a prospective, randomized study, Himpe and colleagues reported the usefulness and safety of succinyl-linked gelatin as priming solution during coronary artery revascularization [25]. Our findings are in agreement with this study. Although we did not investigate the effects of MFG on blood clotting and haemostasis, we found no influence of MFG on postoperative blood loss and blood transfusion. The strong oncotic activity, relatively short effect (3–4 h), dose limitation solely by dilution and the low price of MFG in comparison with other artificial colloids suggest that it is suitable for short-term plasma substitution treatment.

So far, studies dealing with the contents of priming solutions have failed to provide significant clinical advantages for colloid priming compared with crystalloid priming [5–7], as the majority of patients tolerate CPB well, which makes it difficult to measure a clinical response. Furthermore, in our hospital, low-risk patients who underwent elective coronary artery surgery were usually discharged from the ICU the morning after operation, which was also the case for all but one patient in the present study. For that reason, ICU stay is not a useful marker of postoperative recovery. As an alternative approach to determining differences in postoperative clinical performance, we previously introduced the use of a score system based on face validity [18]. The score is composed of three variables of equal weight, all more or less related to the systemic inflammatory response to CPB. A favourable score was calculated in patients treated with colloid priming in comparison with those treated with crystalloid priming, while none of the components of the score differed significantly between groups. This indicates that, even after low-risk coronary artery surgery, the postoperative clinical recovery could be improved in patients treated with a normal COP perfusion. The predictive value of the score is denoted by the significant correlation that was calculated between the score and hospital stay.

Discharge from hospital occurred earlier in the colloid group. Patients had to fulfil criteria of mobility and independence before they were discharged to the referring cardiologist. As illustrated by the regression analysis, CPB time, fluid balance during operation and postoperative $P\text{O}_2/F\text{I}_{\text{O}_2}$ ratio were independent factors that predicted postoperative hospital stay. As normal COP perfusion resulted in a significantly decreased fluid balance, the impact of colloid prime on hospital stay was confirmed.

Acknowledgements

This study was supported by a grant from NPBI BV, Emmer-Compascuum, The Netherlands and B. Braun Melsungen AG, Germany. The help of K. Joop, S. van der Kroft, E. H. Slaats, A. Eerenberg and C. E. Hack in the measurement of biochemical data is gratefully acknowledged.

References

1. Sanchez de Leon R, Paterson JL, Sykes MK. Changes in colloids osmotic pressure and plasma albumin concentration associated with extracorporeal circulation. *British Journal of Anaesthesia* 1982; **54**: 465–474.
2. Tobias MA. Choice of priming fluids. In: Taylor KM, ed. *Cardiopulmonary Bypass: Principles and Management*. London: Chapman and Hall, 1986; 221–248.
3. Beattie HW, Evans G, Garnett ES, Regoeczi E, Webber CE, Wong K-L. Albumin and water fluxes during cardiopulmonary bypass. *Journal of Thoracic and Cardiovascular Surgery* 1974; **67**: 926–931.
4. Hoeft A, Korb H, Mehlhorn U, Stephan H, Sonntag H. Priming of cardiopulmonary bypass with human albumin or Ringer lactate: effect on colloid osmotic pressure and extravascular lung water. *British Journal of Anaesthesia* 1991; **66**: 73–80.
5. Öhqvist G, Settergen G, Bergström K, Lundberg S. Plasma colloid osmotic pressure during open-heart surgery using non-colloid or colloid priming solution in the extracorporeal circuit. *Scandinavian Journal of Thoracic and Cardiovascular Surgery* 1981; **15**: 251–255.
6. Sade RM, Stroud MR, Crawford FA, Cratz JM, Dearing JP, Bartles DM. A prospective randomized study of hydroxyethyl starch, albumin and lactated Ringer's solution as priming fluid for cardiopulmonary bypass. *Journal of Thoracic and Cardiovascular Surgery* 1985; **89**: 713–722.
7. D'Ambra MN, Philbin DM. Colloids should not be added to the pump prime. *Journal of Cardiothoracic Anesthesia* 1990; **4**: 406–408.
8. Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Chenoweth DE, Pacifico AD. Complement and the damaging effects of cardiopulmonary bypass. *Journal of Thoracic and Cardiovascular Surgery* 1983; **86**: 845–857.
9. Westaby S. Organ dysfunction after cardiopulmonary bypass. A systemic inflammatory reaction initiated by the extracorporeal circuit. *Intensive Care Medicine* 1987; **13**: 89–95.
10. Rocke DA, Graffin SL, Wells MT, Koen Y, Brock-Utine JC. Endotoxemia associated with cardiopulmonary bypass. *Journal of Thoracic and Cardiovascular Surgery* 1987; **93**: 832–837.
11. Mollnes Te, Videm V, Gotze O, Harboe M, Opperman M. Formation of C5a during cardiopulmonary bypass: inhibition by precoating with heparin. *Annals of Thoracic Surgery* 1991; **52**: 92–97.
12. Gu YJ, van Oeveren W, Akkerman C, Boonstra PW, Huyzen RJ, Wildevuur ChRH. Heparin-coated circuits reduce the inflammatory response to cardiopulmonary bypass. *Annals of Thoracic Surgery* 1993; **55**: 917–922.
13. Fosse E, Moen O, Johnson E, Semb G, Brockmeier V, Mollnes TE, Fagerhol MK, Venge P. Reduced complement and granulocyte activation with heparin-coated cardiopulmonary bypass. *Annals of Thoracic Surgery* 1994; **58**: 472–477.
14. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977; **1**: 466–469.
15. Sturk A, Janssen ME, Muylaert FR, Joop K, Thomas LLM, Cate ten JW. Endotoxin testing in blood. *Progress in Clinical Biological Research* 1987; **231**: 371–385.
16. Novitsky TJ. Limulus amoebocyte lysate (LAL) detection of endotoxin in human blood. *Journal of Endotoxin Research* 1994; **1**: 253–263.
17. Feinstein AR. The evaluation of validity. In: Feinstein AR, ed. *Clinimetrics*, 1st Edn. New Haven, London: Yale University Press, 1987; 141–166.
18. Jansen PGM, Velthuis te H, Huybregts MAJM, Paulus R, Bulder ER, Van der Spoel HI, Bezemer PD, Slaats EH, Eijsman L, Wildevuur CHRH. Reduced complement activation and improved postoperative performance after cardiopulmonary bypass with heparin-coated circuits. *Journal of Thoracic and Cardiovascular Surgery* 1995; **110**: 829–834.
19. Gabel JC, Drake RE. Pulmonary capillary wedge pressure and permeability. *Critical Care Medicine* 1979; **7**: 92–97.
20. Jansen, PGM, Velthuis te H, Oudemans-van Straaten HM, Bulder ER, Van Deventer SJH, Sturk A, Eijsman L, Wildevuur CHRH. Perfusion-related factors of endotoxin release during cardiopulmonary bypass. *European Journal of Cardiothoracic Surgery* 1994; **8**: 125–129.
21. Borowiec J, Thelin S, Bagge L, Nillson L, Venge P, Hansson HE. Heparin-coated circuits reduce activation of granulocytes during cardiopulmonary bypass. *Journal of Thoracic and Cardiovascular Surgery* 1992; **104**: 642–647.
22. Cavarocchi NC, Schaff HV, Orszulak TA, Homburger HA, Schnell WA, Pluth JR. Evidence for complement activation by protamine–heparin interaction after cardiopulmonary bypass. *Surgery* 1985; **98**: 525–530.
23. Quon CY. Clinical pharmacokinetics and pharmacodynamics of colloidal plasma volume expanders. *Journal of Cardiothoracic Anesthesia* 1988; **2**: 12–23.
24. London MJ. Plasma volume expansion in cardiovascular surgery: practical realities, theoretical concerns. *Journal of Cardiothoracic Anesthesia* 1988; **2**: 39–49.
25. Himpe D, Van Cauwelaert P, Neels H, Stinkens D, Van Den Fonteyne F, Theunissen W, Muylaert P, Hermans C, Goossens G, Moeskops, J. Van Hoof J, Alleman J, Adriaensen H. Priming solutions for cardiopulmonary bypass: comparison of three colloids. *Journal of Cardiothoracic and Vascular Anesthesia* 1991; **5**: 457–466.

British Journal of Anaesthesia 1996; **76**: 20–22

Pupil changes during cardiopulmonary bypass

G. C. FLETCHER, A. J. ASBURY AND J. H. BROWN

Summary

Pupil diameter is used during anaesthesia to assess depth of anaesthesia and indicate cerebral hypoxia. This is especially so during cardiac bypass when other autonomic signs cannot be monitored. We have used a pupillometer to determine the effect of cardiopulmonary bypass on the pupil. We have also investigated if any effect was caused by washout of opioid from the central nervous system by allocating patients to one of two groups: in one the bypass pump was preloaded with fentanyl, in the other with 0.9% saline. Cardiopulmonary bypass caused pupil dilatation of between 17% and 53%, which was unaffected by preloading the bypass pump with fentanyl. This effect lasted for the duration of the study, which ended 30 min after the start of cardiopulmonary bypass. Sympathetic nervous system reflexes and hypothermia may account for this observation, but further research is necessary to exclude other contributory factors. (*Br. J. Anaesth.* 1996; **76**: 20–22)

Key words

Heart, cardiopulmonary bypass. Equipment, pupillometer. Measurement techniques, pupil diameter.

Cardiac anaesthetists are likely to inspect the pupils at several stages during operation and especially during the bypass phase. Subjective assessment of pupil size has been used as one component to estimate depth of anaesthesia [1]. Increasing concern regarding postoperative morbidity is now evident [2, 3] and has focused attention on possible predictive factors, such as alterations in pupil diameter and reactivity [4].

There are few publications on the effect of cardiopulmonary bypass (CPB) on the eye. One of these has described a surprising increase in intraocular pressure (IOP) [5]. The pupillary response to the commencement of CPB has never been documented.

Many physiological and pharmacological factors affect pupil diameter [6, 7], including opioids, anticholinergics, ganglion blockers, sympathomimetics, histamine and steroids. However, the sudden change in so many variables which occurs on starting CPB makes speculation on the resulting pupillary changes unproductive.

A recently developed pupillometer [8] which is robust, easy to use and accurate (0.1 mm) now permits pupillary changes, perhaps previously undetected, to be observed. The aim of this study was twofold: first, to record pupil changes which occur when patients undergo CPB. It was postulated that any change in pupil diameter may be the result of a washout effect of the bypass prime solution on the opioid in the Edinger–Westphal nucleus. Therefore, our second aim was to determine if preloading the bypass pump with fentanyl affected the observed pupil changes.

Patients and methods

Local hospital Ethics Committee approval was obtained and informed consent was given by all participating patients.

Observations of pupil size were carried out in 20 patients, aged 44–69 yr. Eye colour was noted as this has been shown to affect pupil reactivity. Patients were premedicated with lorazepam 2–3 mg the night before and 2–3 mg on the morning of operation. The anaesthetic technique was similar in all patients. Anaesthesia was induced with fentanyl 5 μg kg^{-1} i.v. and propofol, delivered from a target-controlled infusion pump set to infuse to a target of 1–3 μg ml^{-1} [9]. All patients were given pancuronium 0.2 mg kg^{-1} and anaesthesia was maintained with an infusion of fentanyl of 10 μg kg^{-1} h^{-1} (to a total of 30 μg kg^{-1}) and a target-controlled propofol infusion [9]. The lungs were ventilated with an air–oxygen mix ($F\text{I}_{O_2}$ of 0.4). Arterial pressures and central venous pressures were monitored by invasive techniques. A further bolus of fentanyl 5 μg kg^{-1} was given just before incision.

In all cases the extracorporeal circulation involved a Cobe CMS, flat sheet membrane oxygenator primed with Hartmann's solution 2000 ml, heparin 8000 u., potassium chloride 15 mmol, sodium bicarbonate 50 mmol, mannitol 10 g and cefuroxime 750 mg. Patients were allocated randomly into one of two groups using opaque envelopes (saline or fentanyl). In group F, fentanyl 5 μg kg^{-1} was injected into the reservoir of the pump before bypass, in the NonF group, an equivalent volume of normal saline was given into the reservoir. The patients were unaware of the group into which they were placed as was the researcher who measured pupil diameter. The cardioplegic solution (St Thomas' solution 700–1000 ml) was given to cause asystole. During

---

G. C. FLETCHER, MB, CHB, FRCA (Clinical Shock Study Group, Department of Anaesthetics); A. J. ASBURY, MB, CHB, FRCA, PHD, MD, J. H. BROWN, MB, CHB, FRCA (Anaesthetic Department); Western Infirmary, Glasgow G11 6NT. Accepted for publication: June 30, 1995.

Correspondence to G.C.F.

bypass methoxamine i.v. was given to maintain mean arterial pressure greater than 40 mm Hg. At the surgeons' request, 16 patients were cooled to a temperature of 28 °C and four were cooled to 30 °C.

Pre-bypass pupil diameter was recorded during the last minutes before commencing CPB. Readings were then recorded at 30 s, and at 1, 3, 5, 10, 15, 20 and 30 min thereafter.

The Mann–Whitney *U* test in Minitab version 9.2 was used to assess statistical significance between the independent groups and the Wilcoxon signed rank sum test was used for intra-group comparison. Significance was taken at $P < 0.05$.

Results

There were 17 males and three females in the study. Of these patients, 18 were undergoing coronary artery bypass graft, one mitral valve repair and one aortic valve repair. None of the patients had an eye disease other than being long-sighted.

The ages of the patients in the two groups (F and NonF) were not significantly different ($P < 0.05$). Median age in group F was 59 (interquartile range 51.75–65.25) yr and in group NonF 59 (53.75–63.75) yr. Thirteen patients had blue eyes, three brown, two green and two grey. The time to commencement of CPB varied between 50 and 140 min.

There was a significant increase in pupil diameter ($P < 0.001$) compared with pre-bypass size at all times of measurement after the start of CPB (fig. 1). The time of maximum pupil dilatation was 5 min when median dilatation was 0.4 mm (interquartile range 0.3–0.5 mm). Maximum pupil size observed in any one patient was 0.9 mm and the minimum was 0.3 mm. The magnitude of the observed increase in pupil diameter during CPB was not significantly affected by preloading the bypass pump with fentanyl (fig. 2). The population size was too small to make inferences about the effect of eye colour, although the mean pre-bypass diameter and the mean maximum change in diameter for each eye colour is shown in table 1.

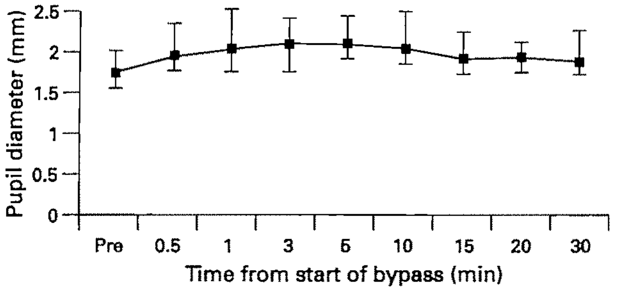


Figure 1 Median (interquartile range) pupil diameter before (Pre) and after commencement of cardiopulmonary bypass.

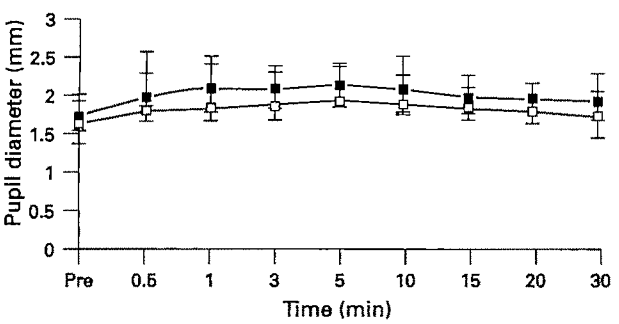


Figure 2 Median (interquartile range) pupil diameter before (Pre) and after commencement of cardiopulmonary bypass in patients whose bypass pump was preloaded with fentanyl (■) or 0.9 % saline (□).

Table 1 Effect of eye colour on the changes in pupil diameter during CPB

Eye colour	No. of patients	Mean pre-bypass pupil diameter (mm)	Mean maximum pupil dilatation (mm)
Blue	13	1.76	0.52
Green	2	1.35	0.45
Brown	3	1.73	0.43
Grey	2	2.05	0.4

One patient developed bilateral conjunctivitis after operation which was considered to be unlikely to be related to the study as only one eye was used for pupil measurements, and nothing came into contact with the surface of the eye.

Discussion

During general anaesthesia there are variations in pupil size [6, 7] and these changes tend to be more pronounced when autonomically active drugs, opioids and central nervous system depressants are given. Such effects occur throughout cardiac anaesthesia, but the sustained and reproducible pattern of pupil dilatation which we have observed during CPB is likely to depend on other physiological variables.

Patients in the study received moderate doses of fentanyl and the mean pre-bypass pupil diameter of 1.75 mm correlates with the effects of a bolus dose of fentanyl to an anaesthetized patient, when mean pupil diameter is reduced from approximately 3.0 to 2.0 mm [10]. Opioids are thought to affect the pupil by reducing cortical inhibition of the Edinger–Westphal nucleus. Binding of fentanyl to receptors in this area might be influenced by the sudden change in plasma concentration as the crystalloid prime flushes through the body. However, this is unlikely as the changes in pupil diameter in the group which had the bypass prime solution preloaded with fentanyl did not differ significantly from those in which the pump was preloaded with saline.

Hypothermia itself is known to dilate the pupils [11] and also reduce IOP. This factor may have played a part in causing the observed pupil dilatation. Investigation of patients undergoing normothermic CPB would help to clarify this.

Autonomic effects on the pupil, mediated via the ciliary ganglion, are obvious in conscious people, and in ophthalmic surgery direct effects of topical autonomically active drugs are used to good effect [12]. During CPB, it is likely that there is both a neurotransmitter and a neuroendocrine response caused by emptying of the atria of the heart and a tendency for a reduction in mean arterial pressure. Measurements of plasma catecholamine concentrations have shown that during CPB plasma noradrenaline concentration increases to a maximum at 60 min and dopamine concentrations increase by 500% at 15 min and then diminish over the next 45 min [13]. In this context it is worth noting the results of Von Sallmann and Lowenstein who used electrode stimulation of the ventral zone of the hypothalamus in cats to mimic the effects of diffuse sympathetic nervous system discharge [14]. They found that IOP increased, but did not comment on any effects on the pupil. It might be expected that a central sympathetic response to the sudden hypotension of CPB would produce much larger increases in pupil diameter than we have observed. Also, the corresponding increase in IOP described by Stellpflug and colleagues [5] was of only a moderate degree. An explanation may be that pupil reactivity is attenuated by the central opioid effect, and hypotension, while triggering the sympathetic nervous system to increase IOP, itself tends to lower IOP [15].

Although sympathetic activity provides a likely explanation for the observed increase in pupil diameter associated with CPB, other physiological variables may play a part [16–21]. There was also a source of error in this study as a result of reading the pupillometer.

Acknowledgement

We thank Dr S. Hickey for his ideas and assistance during this study.

References

1. Boldt J, von Bormann B, Kling D, Russ W, Ratthey K, Hempelmann G. Low dose fentanyl analgesia modified by calcium channel blockers in cardiac surgery. *European Journal of Anaesthesiology* 1987; **4**: 387–394.
2. Shaw PJ, Bates D, Niall EF, Cartlidge NEF, French JM, Heaviside D, Julian DG, Shaw DA. Neurologic and neuropsychological morbidity following major surgery: comparison of coronary artery bypass and peripheral vascular surgery. *Stroke* 1987; **18**: 700–707.
3. Shaw PJ, Bates D, Cartlidge NEF, Heaviside D, French JM, Julian DG, Shaw DA. Neuro-ophthalmological complications of coronary artery bypass surgery. *Acta Neurologica Scandinavica* 1987; **76**: 1–7.
4. Woodall NM, Maryniak JK, Gilston A. Pupillary signs during cardiac surgery. Their use in the prediction of major cerebral deficit following cardiopulmonary bypass. *Anaesthesia* 1989; **44**: 885–888.
5. Stellpflug H, Busse M, Niedermeier M, Dittrich H. Ocular alterations during extracorporeal circulation. *Ophthalmologica (Basel)* 1979; **179**: 249–257.
6. Larson MD. Dilation of the pupil in human subjects after intravenous thiopental. *Anesthesiology* 1981; **54**: 246–249.
7. Rawstron RE, Hutchinson BR. Pupillary and circulatory changes at the termination of relaxant anaesthesia. *British Journal of Anaesthesia* 1963; **35**: 795–803.
8. Asbury AJ, Lear GA, Wortley D. Pupillometer for use during anaesthesia. *Anaesthesia* 1984; **39**: 908–910.
9. Kenny GN, White M. A portable target controlled propofol infusion system. *International Journal of Clinical Monitoring and Computing* 1992; **9**: 179–182.
10. Asbury AJ. Pupil response to alfentanil and fentanyl. A study in patients anaesthetised with halothane. *Anaesthesia* 1986; **41**: 717–720.
11. Feiss P, Mora C, Devalois B, Gobeaux R, Christides C. Accidental deep hypothermia and cardiac arrest, treated by cardiopulmonary bypass. *Annales Francaises d'Anesthesie et de Reanimation* 1987; **6**: 217–218.
12. Alfonso E, Abelson MB, Smith LM. Pharmacologic pupillary modulation in the perioperative period. *Journal of Cataract and Refractive Surgery* 1988; **14**: 78–80.
13. Sebel PS, Bovill JG, Schellekens APM. Hormonal responses to high-dose fentanyl anaesthesia. A study in patients undergoing cardiac surgery. *British Journal of Anaesthesia* 1981; **53**: 941–947.
14. Von Sallmann L, Lowenstein O. Responses of intraocular pressure, blood pressure and cutaneous vessels to electrical stimulation in the diencephalon. *American Journal of Ophthalmology* 1955; **39**: 11–29.
15. Macri FJ. Vascular pressure relationships and the intraocular pressure. *Archives of Ophthalmology* 1961; **65**: 571–574.
16. Smith RB, Aass, AA, Nemoto EM. Intraocular and intracranial pressure during respiratory alkalosis and acidosis. *British Journal of Anaesthesia* 1981; **53**: 967–971.
17. Duncalf D, Weitzner SW. The influence of ventilation and hypercapnia on intraocular pressure during anesthesia. *Anesthesia and Analgesia* 1963; **42**: 232–246.
18. Cunningham AJ. Intraocular pressure—physiology and implications for anaesthetic management. *Canadian Anaesthetists Society Journal* 1986; **33**: 195–208.
19. Marcus DF, Krupin T, Podos SM, Becker B. The effect of exercise on intraocular pressure. 1. Human beings. *Investigative Ophthalmology* 1970; **9**: 749–752.
20. Tsukahara S, Sasaki T, Yamabayashi S, Furuta M, Ushiyama M, Yamamoto T. Effect of alpha-human atrial natriuretic peptides on intraocular pressure in normal albino rabbits. *Ophthalmologica (Basel)* 1988; **197**: 104–109.
21. Goh Y, Nakajima M, Azuma I, Hayaishi O. Prostaglandin D2 reduces intraocular pressure. *British Journal of Ophthalmology* 1988; **72**: 461–464.

British Journal of Anaesthesia 1996; **76**: 23–28

Vecuronium infusion requirements in paediatric patients in intensive care units: the use of acceleromyography

U. M. HODGES

Summary

Neuromuscular blocking drugs in intensive care units (ICU) may cause complications, including prolonged neuromuscular block as a result of overdosage and post-ventilation muscle weakness. These may be increased by using inappropriately high infusion rates for infants, in whom published studies are scarce, and by failure to monitor neuromuscular block. There is little ICU experience of acceleromyography, which may permit more reliable monitoring. To determine appropriate vecuronium infusion rates, 12 neonates/infants (median age 4 (interquartile range (IQR) 2–5) months) and 18 children (median age 3.07 (2–10) yr) were studied. The vecuronium infusion rate was adjusted to maintain train-of-four (TOF) at 1 response using the TOFguard accelerometer. Recovery time was measured from cessation of infusion until spontaneous TOF ratio recovery of 0.7. Neonates and infants required 45% less vecuronium (mean infusion rate 54.7 (SEM 4.23) $\mu g\ kg^{-1}\ h^{-1}$) than older children (98.7 (7.07) $\mu g\ kg^{-1}\ h^{-1}$) and had faster recovery to 70% T4/T1 (45 (IQR 20–51) min *vs* 65 (55–103) min), with no evidence of prolonged weakness. Routine monitoring of neuromuscular block in ICU is essential; acceleromyography is convenient and reliable. (*Br. J. Anaesth.* 1996; **76**: 23–28)

Key words

Monitoring, neuromuscular function. Measurement techniques, acceleromyography. Neuromuscular block, vecuronium. Infants. Intensive care.

Neuromuscular blocking drugs facilitate tracheal intubation and mechanical ventilation. Indications for intensive care use include: maintenance of a motionless state in critically elevated intracranial pressure, tenuous surgical repairs or haemodynamic instability; reduction of oxygen consumption; severe rigidity; and to facilitate procedures [1–3]. However, significant problems are reported and there is little published research into the use of these drugs in paediatric ICU practice. The aim of this study was to determine appropriate vecuronium infusion rates in paediatric ICU and assess acceleromyography for monitoring neuromuscular block in the ICU.

Long-term use of neuromuscular blocking agents may be associated with prolonged weakness, either from prolonged neuromuscular block [4] or from a poorly characterized myopathy [1]. It occurs more commonly with aminosteroid blockers [2] but is found with benzylisoquinolinium compounds [3]. Neuromuscular block may be prolonged by drug overdose or by accumulation of active metabolites [5]. Risk factors for prolonged weakness include hypocalcaemia [6], renal failure [7, 8], metabolic acidosis and hypermagnesaemia [8]. Aminoglycosides prolong the action of neuromuscular blockers by inhibition of presynaptic acetylcholine release and stabilization of postjunctional membranes [9].

Alternatively, tachyphylaxis caused by spontaneous breakdown of atracurium or alterations in protein binding, receptor sites (up-regulation) or volume of distribution may occur. In up-regulation, extrajunctional cholinergic receptor proliferation significantly increases requirements for neuromuscular blockers over time [10]. Other complications of these drugs include histamine release [11] and cardiovascular instability. Atracurium, for example, can cause hypotension and tachycardia at higher doses or on rapid administration [12]. Laudanosine, an atracurium metabolite, may cause seizures in animals [5]. These drugs are also implicated in "ICU psychosis" if ICU staff believe muscular paralysis is a calm, painless state not requiring extra analgesia/sedation [13, 14].

One contributory factor in paediatric ICU may be lack of published research, so that inappropriately high infusion rates are used for infants, leading to overdosage, particularly when neuromuscular function is not monitored. The standard ICU regimen for vecuronium is a bolus of 0.1 $\mu g\ kg^{-1}$, followed by 60–600 $\mu g\ kg^{-1}\ h^{-1}$ [15], but during anaesthesia, neonates and infants need 40% lower infusion rates than older children [16].

Neuromuscular function is rarely well monitored in the ICU [17, 18], thus increasing neuromuscular blocking drug and metabolite accumulation and resulting in reports of prolonged neuromuscular block [19, 20] and, it is suggested, myopathy by "overkilling" the receptors [19]. Monitoring is essential because the critically ill ICU patient has altered pharmacodynamics and pharmacokinetics for

---

U. M. HODGES, BSC (HONS), MB, BS, FRCA, Division of Anaesthetics, United Medical and Dental School, Guy's Hospital, London SE1 9RT. Accepted for publication: September 5, 1995.

Present address: The St Andrew's Centre for Plastic Surgery, St Andrew's Hospital, Stock Road, Billericay, Essex CM12 0BH.

CP25787

drugs, metabolic disturbances and possible drug interactions, making it impossible to predict the dose of neuromuscular blocker required. Judging train-of-four (TOF) response manually (or visually) with certainty is difficult [19, 21] and electromyography and mechanomyography are too cumbersome for routine ICU use. Acceleromyography (with the TOFguard) may be the answer but experience with this technique in the ICU is scarce [19].

The purpose of this study was to determine if neonates/infants require lower infusion rates than older children and to assess the TOFguard accelerometer for paediatric ICU use.

Patients and methods

The study was approved by the Hospital Ethics Committee and informed consent was obtained from the parents of each child. Thirty critically ill patients who were expected to require neuromuscular blocking drugs to assist controlled ventilation were allocated to the study. Sedation was provided throughout by continuous infusion of morphine, midazolam, or both. Routine monitoring of the patients was in accordance with the practice of the unit and included electrocardiogram, direct arterial pressure and temperature measurement (core and peripheral). Arterial blood-gas and electrolyte measurements were carried out twice a day or more often if required, and adjustments made to ventilation and acid–base balance as necessary. The intensive care clinicians used their neuromuscular blocking drug of choice for intubation. The drug given and the dose were recorded.

Neuromuscular function was monitored at the ulnar or tibial nerve using the TOFguard nerve stimulator (Organon Teknika, Cambridge). This makes use of the Newtonian principle that acceleration is proportional to force. The piezoelectric ceramic wafer produces an electrical signal proportional to acceleration. The TOFguard is a compact, microprocessor-controlled, solid state, battery-powered system. It can deliver TOF measurements (supramaximal stimulation TOF 2 Hz), post-tetanic count and, during the recovery phase, TOF ratio. It can be programmed for use in the intensive care unit to monitor long-term relaxation and delivers a TOF stimulation every 5 min. The data are stored and can be played back from a memory card.

After tracheal intubation, neuromuscular block was monitored until the first TOF response (TOF 1) returned, at which time an infusion of vecuronium was started (with a concentration of 0.2–2 mg ml^{-1}), using a Wellmed syringe driver pump. Guidelines for the initial vecuronium infusion rate were as follows: $<$ 1 yr 20–40 μg kg^{-1} h^{-1}; 1–10 yr 100 μg kg^{-1} h^{-1}; $>$ 10 yr 70 μg kg^{-1} h^{-1}. The TOF guard was programmed to deliver a supramaximal TOF stimulus every 5 min. The aim was to maintain TOF at one response. The infusion rate and TOF response were reviewed hourly and if there was no response to TOF stimulation or three or more responses were present, the infusion was reduced or increased by 10% of the original rate until one response was present. If the rate was changed then the TOF response was reviewed at 5–15-min intervals until stable at TOF 1 response. After initial demonstration by the author, the infusions were administered and controlled by the nursing staff. To determine the dose of vecuronium required for each patient and if it altered over time, a manual record was kept hourly of the vecuronium infusion rate, the cumulative dose infused, the TOF response and any other drugs given concurrently. Alterations to the infusion rate were also recorded. In addition, to determine if the time to spontaneous recovery was affected by the age of the patient, duration of infusion or other factors such as renal failure, the time from cessation of infusion to spontaneous recovery of a TOF ratio of 0.7 was recorded.

STATISTICAL ANALYSIS

Two sample Student's *t* test was used for parametric data (infusion rates) and Mann–Whitney *U* test for non-parametric data (recovery times) together with regression analysis of recovery times (Minitab PC version release 8) [22].

Results

Thirty patients were studied. The range of clinical conditions included pneumonia (six patients), asthma (one), head injury (nine), smoke inhalation (one), bronchiolitis (one), laryngotracheitis (one) and postoperative cardiac surgery (11). There were 12 patients aged less than 1 yr (median 4 (interquartile range (IQR) 2–5) months) and 18 children aged over 1 yr (3.07 (2–10) yr). The duration of infusions varied between 6–187 h (median 64.5 (IQR 30–81.5) h. Recovery times were available for 10 infants and 17 children (one neonate died during the study, one was transferred to another hospital and one infusion was discontinued after 6 h without the recovery time being recorded). Four patients developed renal failure requiring peritoneal dialysis during the study.

There was an age-dependent statistically significant difference in vecuronium requirements. The mean infusion rate for those less than 1 yr was 54.7 (SEM 4.23) μg kg^{-1} h^{-1}, while for children over 1 yr it was 98.7 (7.07) μg kg^{-1} h^{-1} with 95% confidence interval (CI) of 24.8–63; the *t* test statistic was 4.7, with 28 degrees of freedom (df) and an associated *P* value of 0.0001 (table 1).

There was also an age-dependent statistically significant difference in recovery times between the

Table 1 Mean (SEM) infusion rate and median (IQR) recovery times to TOF ratio $>$ 0.7, for patients less than or more than 1 yr of age

	Under 1 yr	Over 1 yr	*P*
Infusion rate (μg kg^{-1} h^{-1})	54.73 (4.23)	98.7 (7.07)	0.0001
Recovery (min)	45 (20–51)	65 (55–103)	0.0019

Table 2 Details of patients in renal failure requiring peritoneal dialysis. TOF = Repaired tetralogy of Fallot, ALCA = anomalous left coronary artery

Patient No.	Age (yr)	Diagnosis	Infusion rate (µg kg^{-1} h^{-1})	Duration (h)	Recovery (min)
1	0.11	TOF	37	76	47
2	2.09	TOF	74.3	46	20
3	2.03	TOF	126.5	22	55
4	0.03	ALCA	30.7	187	Died

Table 3 Mean (SEM) duration of "short" and "long" infusions, together with patient details. There was no significant difference between median (IQR) age or weight, mean (SEM) infusion rate or median (IQR) recovery time for the two groups

	"Short" infusions	"Long" infusions
Duration (h)	26.64	94.75
	(3.76)	(9.76)
Age (yr)	1.5	1.5
	(0.04–4)	(0.04–5)
Weight (kg)	11.95	11.8
	(5.32–18.25)	(4.99–24.85)
Infusion rate (µg kg^{-1} h^{-1})	79.9	82.2
	(8.56)	(8.71)
Recovery time (min)	55	60
	(24–64)	(47–100)

two groups. The median recovery time was 45 (20–51) min in neonates/infants and 65 (55–103) min in older children, with 95% CI of 10–60 and an associated P value of 0.0019 (table 1).

Two infants and two older children required peritoneal dialysis for renal failure (table 2). While the infusion rate for infants was lower than the sample mean, there was no apparent difference in infusion requirements for older children. None of the patients with renal failure demonstrated prolongation of recovery from the sample median. On re-analysing the data for vecuronium infusion requirements, without the four patients in renal failure, there was still an age-dependent statistically significant difference ($P = 0.0007$).

The regression equation for recovery times for all patients overall against duration of infusion was: recovery = 35.7 + 0.456 duration, with R^2(adj) = 20.9% and $P = 0.006$. This might suggest that time to spontaneous recovery of a TOF ratio > 0.7 is related to the duration of infusion. However, the equation is highly influenced by the only outlier. This patient became very active shortly after the infusion of vecuronium was discontinued. When a child is very active it is difficult to obtain a TOFguard reading, even when obvious clinical signs of recovery, such as sustained headlift, are being demonstrated. Until nursing stimulation ceased and there was adequate sedation, there was no accurate TOF result. The recovery time finally obtained therefore reflected the time to finishing nursing activities rather than spontaneous recovery. If the analysis is repeated without this value, the equation becomes: recovery = 44.8 + 0.292 duration, with R^2(adj) = 4.9% and $P = 0.148$, that is there would appear to be no significant relationship between the duration of infusion and recovery time. There was no evidence of prolonged weakness in any of the patients or of drugs such as aminoglycosides or steroids influencing the time to recovery.

This study also found no evidence of an overall reduction in vecuronium requirements over time to suggest cumulation, or of an increase in requirements which might indicate tachyphylaxis. A regression analysis comparing duration of all infusions against infusion requirements showed no significant relationship. In addition, if the mean infusion rate for the first 6 h of the infusions (79.21 (SEM

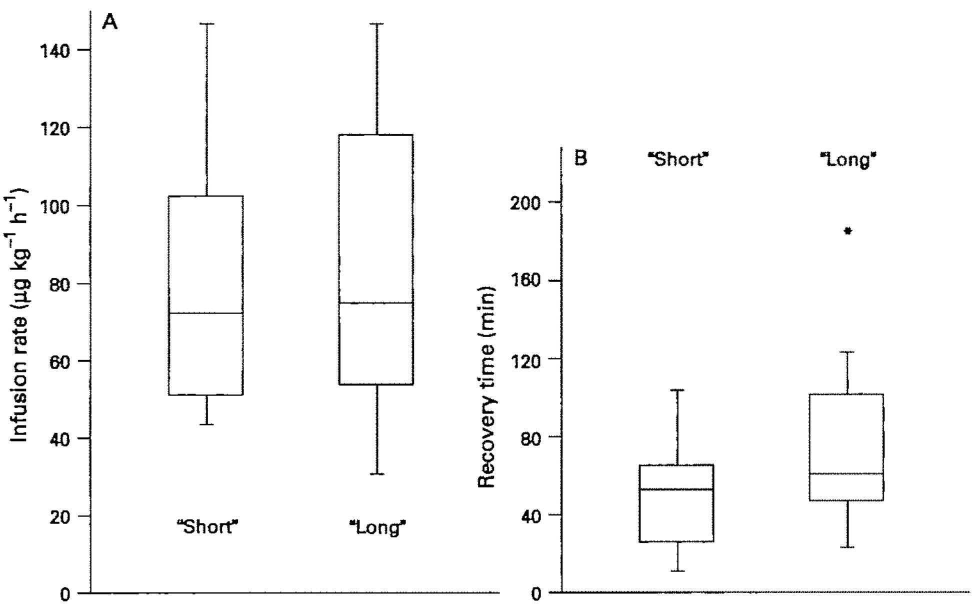


Figure 1 A: Percentile box plot of vecuronium infusion rates for "short" and "long" infusions. B: Percentile box plot of recovery times for short and long infusions. The box shows the difference between the quantiles; the median is indicated as a line and the whiskers show the extremes. The asterisk shows a possible outlier [22]. There was no significant difference in either dosage or recovery times.

6.62) $\mu g\ kg^{-1}\ h^{-1}$) is compared with that for the final 6 h of the infusions (87.86 (7.11) $\mu g\ kg^{-1}\ h^{-1}$), there is no significant difference. For the two age groups the mean infusion rate for patients less than 1 yr was 55.82 (7.38) $\mu g\ kg^{-1}\ h^{-1}$ for the first 6 h compared with 55.36 (3.76) $\mu g\ kg^{-1}\ h^{-1}$ for the final 6 h (ns), while for those over 1 yr, the mean infusion rate was 94.35 (7.97) $\mu g\ kg^{-1}\ h^{-1}$ for the first 6 h compared with 108.88 (8.04) $\mu g\ kg^{-1}\ h^{-1}$ for the final 6 h (ns).

In addition, previous research has mainly analysed data from infusions lasting less than 48 h. In this study there were 14 patients who received infusions for less than 48 h ("short" infusions); these results may be compared with data from the 16 patients who received infusions for longer than 48 h ("long" infusions) (table 3). There was no difference in age or weight between these two groups. Also, there was no significant difference in infusion rates between the two groups (fig. 1A). Recovery times varied between 15 and 105 min in the short infusion group and between 22 and 180 min in the long infusion group (fig. 1B) (ns). The data were re-analysed removing any outliers because of the variation in recovery times seen in both groups. Despite this re-analysis without the 105-min recovery time in the short group and without the 22-min recovery time in the long group, there was still no significant difference between them.

Discussion

In this study there was an age-dependent statistically significant difference in vecuronium requirements in the paediatric ICU. Neonates and infants required 45% less vecuronium than older children.

The neuromuscular effects of bolus doses of vecuronium have been studied previously [23–27], demonstrating an age-dependence of dose and recovery times [23, 26]. Similarly, infusion requirements during fentanyl–nitrous oxide–oxygen anaesthesia have been found to be 40% lower for neonates/infants (62 (SD 15) $\mu g\ kg^{-1}\ h^{-1}$) than for children aged 3–10 yr (154 (49) $\mu g\ kg^{-1}\ h^{-1}$) [16]. The ED_{95} of vecuronium for all patients less than 1 yr, including neonates, is 47 $\mu g\ kg^{-1}$ and is the product of the distribution volume and its plasma concentration [26]. Neuromuscular blocking drugs are distributed to the extracellular fluid volume which is approximately 44% of body weight at birth; only approaching the adult value of 22% at 1 yr of age [28]. In neonates and infants, therefore, it is concluded that during anaesthesia, neuromuscular block is reached at a lower total plasma concentration of vecuronium than in older children. The lower serum protein concentrations in neonates/infants may also indicate that lower total plasma concentrations of neuromuscular blocking drugs are needed.

There are few studies on vecuronium infusions in paediatric ICU and none comparing neonates/infants with children. An infusion rate of 66 (37) $\mu g\ kg^{-1}\ h^{-1}$ is reported but in only 12 patients (mean age 35.5 months (range 3 weeks to 13.5 yr)), with no attempt to analyse by age and with infusions of only 12 h in duration [29]. Another report of four neonates, three infants and eight children unfortunately combined the results for infants and children (mean dose of 140 (SD 0.05) $\mu g\ kg^{-1}\ h^{-1}$) to compare them with neonates (110 (0.05) $\mu g\ kg^{-1}\ h^{-1}$) [17], thus making comparison with studies during anaesthesia difficult. It suggested that the infusion rates were higher than those during anaesthesia because patients required a longer period of lung ventilation. It may be argued, however, that they reflect, instead, the relatively small sample size; that is, given the wide inter-individual variation in requirements seen in the present study (30.7–147 $\mu g\ kg^{-1}\ h^{-1}$), their smaller numbers reflect the higher end of the range, rather than being a true population sample. Also, only three infusions lasted longer than 48 h, unlike the present study where 16 of 30 infusions lasted longer than 48 h. The present study confirms the findings from short infusions and bolus usage of age-dependence in the vecuronium dose–response curve.

In addition, the present study showed an age-dependent difference in recovery times between neonates/infants and older children, with faster recovery in the former. Others, however, have found an age-dependent prolongation of spontaneous recovery in neonates and infants, arguing that this results from their greater distribution volume [30]. This study is widely quoted to show that vecuronium has a longer duration of action in neonates/infants than in older children. Why then is the opposite the case in this present study? The age-dependent prolongation of spontaneous recovery quoted refers to the time to full restoration of TOF 1 response. When TOF 1 response is restored, they also found that TOF ratio recovered faster in younger patients, suggesting proportionally more rapid restoration of muscle strength [30]. This age-dependence of TOF recovery has not been studied widely.

Another question addressed by this study was whether or not spontaneous recovery is affected by factors such as renal failure, as previously suggested [8, 31–33]. The four patients requiring peritoneal dialysis for renal failure did not have prolonged recovery but rather, in infants at least, needed smaller doses. Unlike previous reports, this study set out to adjust the infusion rate to maintain TOF at 1 response, as a fixed-dose infusion regimen in the presence of renal failure has been shown to lead to gradually increasing block [31]. Another study of seven patients with renal failure found prolonged neuromuscular block, lasting from 6 h to more than 7 days after termination of vecuronium [8]. However, neuromuscular function in these patients was monitored after the vecuronium infusion was discontinued. Those patients who, despite being in renal failure, did not develop prolonged block had received significantly smaller daily doses of vecuronium (median 0.29 (range 0.23–0.42) $mg\ kg^{-1}$) than those who did (0.65 (0.48–2.29) $mg\ kg^{-1}$) ($P < 0.05$). Other studies have shown that patients with chronic renal failure have increased sensitivity to the neuromuscular blocking effects of vecuronium [33]. Initially, the increased sensitivity is offset by the increase in distribution volume so induction doses should be equal to or slightly higher than for patients without renal failure. However, because of the increased sensitivity and a possible decrease in clearance, the maintenance doses need to be reduced. This study tends to confirm these findings.

It has been suggested that with time, tolerance and up-regulation of acetylcholine (ACh) receptors occurs in ICU patients receiving neuromuscular blocking drugs, leading to increased requirements [34]. Other factors leading to up-regulation include upper and lower motor neurone lesions, muscle trauma, burns, immobilization, anticonvulsants and clostridial toxins [35]. On the other hand, it is also proposed that prolonged recovery may occur with decreased infusion rates over time if accumulation of neuromuscular blocking drug or active metabolites occurs [36]. In this study duration of infusion did not appear to affect either the dose required or time to spontaneous recovery; that is, there was no apparent evidence of cumulation or ACh receptor up-regulation, provided infusions were titrated to individual patients. Longer infusions (8–12 weeks) may affect receptors differently [10].

Another potential problem is the development of a poorly characterized myopathy after long infusions, leading to weakness. This was not seen in the present study, despite the presence of factors such as renal failure which are thought to increase its incidence. This may result from the routine use of the nerve stimulator, which made it possible to achieve precise individual dosage of drug, avoiding "overkilling" of the ACh receptor [19, 20].

In conclusion, this study has shown that there is an age-dependent statistically significant difference in vecuronium requirements in the paediatric ICU. Maintaining the correct infusion rate revealed that neonates/infants have a faster spontaneous recovery from TOF 1 response to TOF ratio > 0.7 than older children. We also showed that renal failure does not prolong recovery when patients are fully monitored, with infusion rates adjusted to maintain TOF 1 response, but suggest that requirements may need to be reduced. Acceleromyography was a convenient and reliable method for monitoring neuromuscular function in the paediatric ICU.

References

1. Coursin DB, Kelly JS, Prielipp RC. Muscle relaxants in critical care. *Current Opinion in Anesthesiology* 1993; **6**: 341–346.
2. Partridge BL, Abrams JH, Bazemore C, Rubin R. Prolonged neuromuscular blockade after long-term infusion of vecuronium bromide in the intensive care unit. *Critical Care Medicine* 1990; **18**: 1177–1179.
3. Meyer KC, Prielipp RC, Grossman JE, Coursin DB. Prolonged weakness after infusion of atracurium in two intensive care unit patients. *Anesthesia and Analgesia* 1994; **78**: 772–774.
4. Hansen-Flaschen J, Cowen J, Raps EC. Neuromuscular blockade in the ICU. More than we bargained for. *American Review of Respiratory Disease* 1993; **147**: 234–236.
5. Adams LJ. Neuromuscular blocking agents: a pharmacotherapeutic review. *Hospital Pharmacy* 1992; **27**: 391–393, 396–400.
6. Pribble C, Timmons O, Moore M, Gooch J. Risk factors for prolonged weakness after vecuronium infusions in pediatric patients. *Critical Care Medicine* 1995; **23**: A219.
7. Haynes SR, Morton NS. Prolonged neuromuscular blockade with vecuronium in a neonate with renal failure. *Anaesthesia* 1990; **45**: 743–745.
8. Segredo V, Caldwell JE, Matthay MA, Sharma ML, Gruenke LD, Miller RD. Persistent paralysis in critically ill patients after long-term administration of vecuronium. *New England Journal of Medicine* 1992; **327**: 524–528.
9. Sokoll MD, Gergis SD. Antibiotics and neuromuscular function. *Anesthesiology* 1981; **55**: 148–159.
10. Coursin DB, Klasek G, Goelzer SL. Increased requirements for continuously infused vecuronium in critically ill patients. *Anesthesia and Analgesia* 1989; **69**: 518–521.
11. Goudsouzian NG, Young ET, Moss J, Liu LMP. Histamine release during the administration of atracurium or vecuronium in children. *British Journal of Anaesthesia* 1986; **58**: 1229–1233.
12. Isenstein DA, Venner DS, Duggan J. Neuromuscular blockade in the intensive care unit. *Chest* 1992; **102**: 1258–1266.
13. Fiamengo SA, Savarese JJ. Editorial. Use of muscle relaxants in intensive care units. *Critical Care Medicine* 1991; **19**: 1457–1459.
14. Loper KA, Butler S, Nessly M, Wild L. Paralysed with pain: the need for education. *Pain* 1989; **37**: 315–316.
15. Shann F, Duncan A, Butt W, Henning R, Smith M, Tibballs J. *Drug Doses*, 8th Edn. Australia: Collective Pty Ltd, 1994.
16. Meretoja OA. Vecuronium infusion requirements in pediatric patients during fentanyl–N_2O–O_2 anesthesia. *Anesthesia and Analgesia* 1989; **68**: 20–24.
17. Fitzpatrick KTJ, Black GW, Crean PM, Mirakhur RK. Continous vecuronium infusion for prolonged muscle relaxation in children. *Canadian Journal of Anaesthesia* 1991; **38**: 169–174.
18. Hansen-Flaschen JH, Brazinsky S, Basile C, Lanken PN. Use of sedating drugs and neuromuscular blocking agents in patients requiring mechanical ventilation for respiratory failure. A national survey. *Journal of the American Medical Association* 1991; **266**: 2870–2875.
19. Viby-Mogensen J. Monitoring neuromuscular function in the intensive care unit. *Intensive Care Medicine* 1993; **19**: S74–S79.
20. Rudis M, Sikora CA, Angus E, Peterson E, Popovich J, Hyzy R, Zarowitz B. Vecuronium dosing by peripheral nerve stimulation results in lower paralytic doses but does not change recovery time in critically-ill medical patients. *Critical Care Medicine* 1995; **23**: A72.
21. Harper NJN. Neuromuscular blocking drugs: practical aspects of research in the intensive care unit. *Intensive Care Medicine* 1993; **19**: S80–S85.
22. *Minitab Reference Manual PC Version Release 8*. Rosemount PA: Quickset Inc., 1991; 14–4.
23. Fisher DM, Miller RD. Neuromuscular effects of vecuronium (ORG NC45) in infants and children during N_2O halothane anesthesia. *Anesthesiology* 1983; **58**: 519–523.
24. Goudsouzian NG, Martyn JJA, Liu LMP, Gionfriddo M. Safety and efficacy of vecuronium in adolescents and children. *Anesthesia and Analgesia* 1983; **62**: 1083–1088.
25. Meistelman C, Loose JP, Saint-Maurice C, Delleur MM, da Silva GL. Clinical pharmacology of vecuronium in children. Studies during nitrous oxide and halothane in oxygen anaesthesia. *British Journal of Anaesthesia* 1986; **58**: 996–1000.
26. Meretoja OA, Wirtavouri K, Neuvonen PJ. Age dependence of the dose–response curve of vecuronium in pediatric patients during balanced anesthesia. *Anesthesia and Analgesia* 1988; **67**: 21–26.
27. Meretoja OA. Is vecuronium a long-acting neuromuscular blocking agent in neonates and infants? *British Journal of Anaesthesia* 1989; **62**: 184–187.
28. Friis-Hansen B. Body composition during growth. In vivo measurements and biochemical data correlated to differential anatomical growth. *Pediatrics* 1971; **47**: 264–274.
29. Eldadah MK, Newth CJL. Vecuronium by continuous infusion for neuromuscular blockade in infants and children. *Critical Care Medicine* 1989; **17**: 989–992.
30. Kalli I, Meretoja OA. Duration of vecuronium in infants and children anaesthetised without potent inhalation agents. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 29–33.
31. Smith CL, Hunter JM, Jones RS. Vecuronium infusions in

patients with renal failure in an ITU. *Anaesthesia* 1987; **42**: 387–393.

32. Segredo V, Matthay MA, Sharma ML, Gruenke LD, Caldwell JE, Miller RD. Prolonged neuromuscular blockade after long-term administration of vecuronium in two critically ill patients. *Anesthesiology* 1990; **72**: 566–570.
33. Henning RH, Wierda JMKH, Scaf AHJ, Marescau B, De Deyn PP, Agoston S. Increased sensitivity to vecuronium in patients with chronic renal failure. *Drug Investigation* 1993; **5**: 98–107.
34. Hogue CW, Ward JM, Itani MS, Martyn JAJ. Tolerance and upregulation of acetylcholine receptors following chronic infusion of d-tubocurarine. *Journal of Applied Physiology* 1992; **72**: 1326–1331.
35. Martyn JAJ, White DA, Gronert GA, Jaffe RS, Ward JM. Up-and-down regulation of skeletal muscle acetylcholine receptors. Effects of neuromuscular blockers. *Anesthesiology* 1992; **76**: 822–843.
36. Martineau RJ, St-Jean B, Kitts JB, Curran MC, Linday P, Hull KA, Miller DR. Cumulation and reversal with prolonged infusions of atracurium and vecuronium. *Canadian Journal of Anaesthesia* 1992; **39**: 670–676.

British Journal of Anaesthesia 1996; **76**: 29–33

Pharmacokinetics of rocuronium after bolus and continuous infusion during halothane anaesthesia

E. P. McCoy, R. K. Mirakhur, V. R. Maddineni, J. M. K. H. Wierda and J. H. Proost

Summary

We have studied the pharmacokinetics of a single bolus of rocuronium (Org 9426), followed by an infusion, in eight patients during anaesthesia with halothane and nitrous oxide in oxygen. Neuromuscular block was monitored using train-of-four (TOF) stimulation and recording the force of contraction of the adductor pollicis muscle. Rocuronium was administered as an initial bolus dose of 0.45 mg kg^{-1} followed by an infusion adjusted manually to maintain T1 (first response in the TOF) at 10% of control. Mean onset time and time to recovery of T1 to 10% were 72 (SD 19.6) s and 27 (9.6) min, respectively. The infusion rates were stable in 19.8 (6.5) min. The mean requirement for rocuronium for steady state 90% block of T1 was 528 (163.3) µg kg^{-1} h^{-1}. After cessation of surgery the infusion was stopped and patients were allowed to recover spontaneously. The times to attain a T1 of 90% and a TOF ratio of 0.7 were 31 (11.7) min and 36 (7.3) min, respectively. Blood samples were collected for 390 min after cessation of infusion and concentrations of rocuronium and its putative metabolites measured using HPLC. A two-exponential equation was used to describe the pharmacokinetic data. The rate of clearance, mean residence time and volume of distribution at steady state were 3.3 (0.77) ml kg^{-1} min^{-1}, 67.2 (18.8) min and 212.5 (40.1) ml kg^{-1}, respectively. The distribution ($T_{\frac{1}{2}}^{\alpha}$) and elimination ($T_{\frac{1}{2}}^{\beta}$) half-lives were 7.5 (3.33) min and 85.6 (18.4) min, respectively. These values were not significantly different from previously published data for a single bolus dose of rocuronium. (*Br. J. Anaesth.* 1996; **76**: 29–33)

Key words

Neuromuscular block, rocuronium. Pharmacodynamics. Pharmacokinetics, rocuronium. Anaesthetics volatile, halothane.

Rocuronium is a new monoquaternary aminosteroidal non-depolarizing neuromuscular blocking drug with an intermediate duration of action similar to that of vecuronium but with a much faster onset of effect [1–4]. Blockers with an intermediate duration of action, such as vecuronium and atracurium, have previously been shown to be suitable for administration by continuous infusion [5, 6]. Because of its rapid onset and intermediate duration of action, rocuronium has also been found to be suitable for use by continuous infusion [7, 8]. Previous pharmacokinetic studies after single bolus doses have shown the clearance and elimination half-life of rocuronium to be 2.5–3.97 ml kg^{-1} min^{-1} and 104–131 min, respectively [2, 9]. Blockers used over longer periods by infusion may show a progressive decrease in the drug infusion rate because of accumulation of drug in the distribution compartments [10, 11]. In the present study we have therefore estimated the pharmacokinetics of rocuronium when administered as a bolus followed by continuous infusion. The results were compared with previously published data for a single bolus dose [9].

Patients and methods

After obtaining informed consent and approval of the Regional Ethics Committee, we studied eight adult patients, aged 18–65 yr, ASA I and II, undergoing elective surgery lasting more than 1 h. These patients were part of a larger study assessing the use of rocuronium by continuous infusion. None had a renal or hepatic dysfunction or was receiving any medication known to interact with neuromuscular blocking agents. Any patient above 35 % or below 20 % of their ideal body weight was excluded.

After premedication with oral temazepam 10–20 mg, anaesthesia was induced with fentanyl 2–3 µg kg^{-1} and thiopentone 3–5 mg kg^{-1}, and maintained with 66 % nitrous oxide and 0.5 % halothane (inspired) in oxygen and additional doses of fentanyl. Heart rate (from ECG), non-invasive arterial pressure, end-tidal carbon dioxide concentration, oxygen saturation and temperature were monitored routinely. Ventilation was adjusted to maintain end-tidal carbon dioxide concentration at 4.5–5.5 %. Skin temperature over the adductor pollicis muscle was maintained above 32 °C.

E. P. McCoy, FFARCSI, R. K. Mirakhur, MD, FRCA, V. R. Maddineni, MD, PHD, FFARCSI, Department of Anaesthetics, The Queen's University of Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL, Northern Ireland. J. M. K. H. Wierda, MD, PHD, J. H. Proost, PHD, Research Group for Experimental Anaesthesiology and Clinical Pharmacology, University Hospital, Groningen, The Netherlands.
Accepted for publication: August 19, 1995.
Correspondence to R. K. M.

The ulnar nerve was stimulated percutaneously at the wrist with supramaximal stimuli of 0.2 ms duration, in a train-of-four (TOF) mode at 2 Hz every 12 s; the resultant force of contraction of the adductor pollicis muscle was measured and recorded using a force displacement transducer and a neuromuscular function analyser (Myograph 2000, Biometer, Denmark Ltd). After stabilization of control responses over approximately 10 min, patients were given rocuronium 0.45 mg kg^{-1} as a single fast i.v. bolus. The time from the end of injection of the neuromuscular blocker to maximum block (onset time) was measured. Tracheal intubation was carried out when maximum block was present.

An infusion of rocuronium was commenced after recovery of the first response in the TOF (T1) to 10 % of control and its rate adjusted to maintain T1 at 10 %. The initial rate was about 15 μg kg^{-1} min^{-1} (900 μg kg^{-1} h^{-1}). The infusion rate and intensity of block were recorded every 10 min. At the end of surgery the infusion was stopped and the block allowed to recover spontaneously. The times for spontaneous recovery of T1 to 25 %, 75 % and 90 % of control and of the TOF ratio to 0.7 were recorded. Anaesthesia was stopped and the trachea extubated when appropriate.

Venous blood samples (4 ml) were obtained from a dedicated cannula before administration of rocuronium, at 1, 3, 5, 10, 15 and 30 min after administration of the bolus dose, at 5, 10 and 20 min after commencement of the infusion of rocuronium, and at 20-min intervals thereafter, and 1, 3, 5, 10, 15, 30, 60, 90, 150, 210, 270, 330 and 390 min after the infusion was stopped. Samples were also obtained at recovery of T1 to 25 % and when the TOF ratio was 0.7. Samples were collected in lithium heparinized tubes and centrifuged within 4 h. The plasma was acidified with sodium dihydrogen phosphate solution 1 mol $litre^{-1}$ (0.2 ml to every 1.0 ml of plasma) and stored at −18 °C until analysis. Analysis of rocuronium and its putative metabolites, 17-desacetyl rocuronium and 16-*N*-desallyl rocuronium was carried out using high pressure liquid chromatography (HPLC), with 3,17-didesacetyl vecuronium (Org 7402) as the internal standard [12]. The precision (reproducibility) of the method was 8 % over the range 10–100000 ng ml^{-1} for rocuronium, 7 % over 10–25000 ng ml^{-1} for 17-desacetyl rocuronium and 12 % over 10–25000 ng ml^{-1} for desallyl rocuronium. The lower limits of detection were 3, 5 and 15 ng ml^{-1} for rocuronium, 17-desacetyl rocuronium and desallyl rocuronium, respectively.

The plasma concentration–time data were analysed using the program Multifit (JH Proost, University Centre for Pharmacy, Groningen, The Netherlands). It uses standard procedures and pharmacokinetic formulae derived from the literature [13]. The method has been used previously both for single doses and continuous infusions of blockers [2, 9, 14]. Concentration *vs* time data were fitted for each patient to both a two- and three-exponential equation using Marquardt as the minimizing algorithm [15]. The choice between the two- and three-exponential equations was based on the *F* test [16]. The volume of the central compartment (V_c), steady-state distribution volume (V^{ss}), plasma clearance (*Cl*), elimination half-life ($T_{\frac{1}{2}}^{\beta}$) and mean residence time (MRT) were calculated using standard equations. Elimination was assumed to take place from the central compartment and MRT refers to the bolus dose.

The results were compared using a Mann–Whitney test with previously published data obtained after administration of a single bolus dose of rocuronium [9].

Results

Mean age, weight and height of the eight patients (seven male, one female) were 35 (range 18–59) yr, 67 (SD 8.4) (54–80) kg and 167 (4.9) (158–175) cm, respectively.

PHARMACODYNAMIC EFFECTS

Onset time (time from the end of injection to maximum effect) was 72 (SD 19.6) s and all patients attained complete block. The time to recovery of T1 to 10 % was 27 (9.6) min.

The mean rates of infusion required to maintain T1 at 10 %, recorded every 10 min, are given in table 1. There were large individual variations, as demonstrated by the large SD values. The rate was initially high but stabilized at 450–600 μg kg^{-1} h^{-1} in a mean time of 19.8 (6.5) min. The infusion rate showed a reduction from 70 min onwards but there were only two patients in the study beyond this time. The mean infusion rate for all patients over the entire period was 528 (163) μg kg^{-1} h^{-1}. The mean duration of the infusions was 74 (45.1) min (range 40–176 min) and the mean total dose of rocuronium administered was 1.0 (0.18) (0.66–1.18) mg kg^{-1}.

The speed of recovery after the infusions were stopped is shown in table 2. Mean times for recovery of T1 to 25 %, 75 % and 90 % of control were 9.1 (6.3), 26.0 (10.2) and 31.4 (11.7) min, respectively. Recovery index was 17 (6.2) min and the time to recovery of the TOF ratio to 0.7, 36.4 (7.3) min.

PHARMACOKINETICS

Figures 1 and 2 show the plasma concentrations of rocuronium in individual patients and the average for the group during the bolus dose and infusion maintenance, and in the post-infusion period. The plasma concentration decay was fitted (using the whole data set) to a simpler two- rather than a three-exponential equation as there was no significant difference between the two (mean coefficients of variance of 22 % and 17 % for the two- and three-exponential fits, respectively).

The kinetic characteristics are given in table 3. Mean V^{ss}, *Cl*, $T_{\frac{1}{2}}^{\beta}$ and MRT were 212.5 ml kg^{-1}, 3.3 ml kg^{-1} min^{-1}, 85.6 min and 67.2 min, respectively. The values were not significantly different from those obtained previously using a single dose of rocuronium [9]. No metabolites were detected in the plasma of any patient.

Table 1 Rocuronium infusion data (mean (SD) [range])

Time (min)	Infusion rate ($\mu g\ kg^{-1}\ h^{-1}$)	Twitch height (% of control)	No. of patients
0	888 (7) [800–1000]	10 (0) [10–10]	8
10	638 (320) [300–1300]	11 (3.1) [7–17]	8
20	531 (211) [200–800]	9.1 (2.2) [6–14]	8
30	488 (185) [250–900]	9.2 (2.7) [5–14]	8
40	419 (257) [100–1000]	9.4 (2.3) [4–12]	8
50	492 (309) [100–1100]	11 (3.6) [6–16]	6
60	400 (123) [300–600]	10 (0.43) [9–10]	4
70	325 (25) [300–350]	10 (1) [9–11]	2
80	250 (50) [200–300]	8.5 (0.5) [8–9]	2
90	250 (50) [200–300]	9.5 (0.5) [9–10]	2
100	250 (50) [200–300]	10 (0) [10–10]	2
110	250 (50) [200–300]	10 (1) [9–11]	2
120	300 (0) [300–300]	10.5 (0.5) [10–11]	2
130	200 (0) [200–200]	8 (0) [8–8]	1
140	200 (0) [200–200]	8 (0) [8–8]	1
150	200 (0) [200–200]	10 (0) [10–10]	1
160	200 (0) [200–200]	10 (0) [10–10]	1
170	200 (0) [200–200]	14 (0) [14–14]	1

Table 2 Recovery of neuromuscular function after cessation of infusion (mean (SD) [range]) (*7). TOF = Train-of-four ratio, T1 = height of the first response in the TOF, recovery index = time for recovery of T1 from 25 to 75%

Time (min) to recovery of	
T1 to 25%	9.1 (6.3) [5.1–25]
T1 to 75%	26.0 (10.2) [15–44]
T1 to 90%	31.4 (11.7) [17–54]
TOF ratio of 0.7	36.1 (7.3)* [25–47]
Plasma concentration ($ng\ ml^{-1}$)	
at T1 of 25%	1287 (615) [528–2500]
at TOF ratio of 0.7	711 (361.4)* [275–1078]
Recovery index (min)	17 (6.2) [9–31]

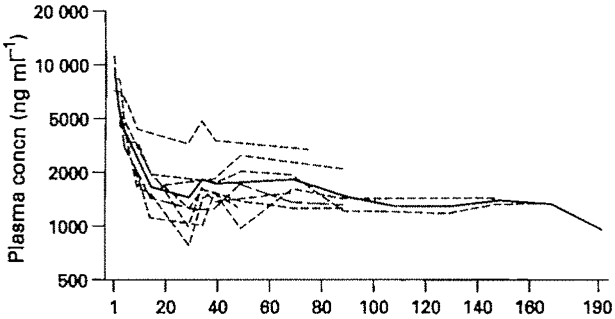


Figure 1 Plasma concentrations of rocuronium after administration of a bolus dose of 0.45 mg kg^{-1} and during maintenance by infusion in each of the eight patients. Thick line = mean for the group at each time.

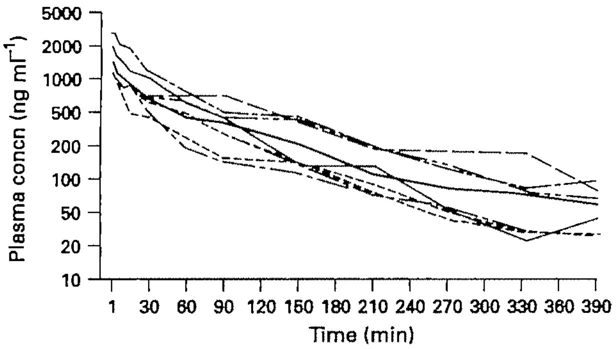


Figure 2 Plasma concentrations of rocuronium after cessation of infusion of rocuronium in each of the eight patients. Thick line = mean for the group at each time.

Table 3 Main pharmacokinetic variables (mean (SD) [range]). V_c (ml kg^{-1}) = Volume of the central compartment; V^{ss} (ml kg^{-1}) = volume of distribution at steady state; $T_{\frac{1}{2}}{}^{\alpha}$ and $T_{\frac{1}{2}}{}^{\beta}$ (min) = distribution and elimination half-lives; *Cl* (ml kg^{-1} min^{-1}) = clearance; MRT (min) = mean residence time (*Data for single dose from Cooper and colleagues [9])

	Bolus and infusion (present study) ($n = 8$)	Single dose* ($n = 9$)
V_c	62.2 (7.92) [48.2–71.4]	38.5 (21.1) [10.54–78.12]
V^{ss}	212.5 (40.1) [152.1–302.8]	207.1 (48.9) [151.1–287.4]
$T_{\frac{1}{2}}{}^{\alpha}$	7.5 (3.33) [3.74–15.52]	14.8 (5.5) [7.99–23.2]
$T_{\frac{1}{2}}{}^{\beta}$	85.6 (18.4) [53.7–108.5]	97.2 (26.4) [67.94–141.72]
Cl	3.3 (0.77) [1.97–4.55]	3.7 (1.4) [2.45–6.05]
MRT	67.2 (18.8) [47–96.6]	58.3 (9.6) [38.41–66.17]

Discussion

The present study has confirmed that rocuronium is a neuromuscular blocking drug with a rapid onset of action, thought to be a result of its low potency, and is in keeping with other reports of its rapid onset of effect [1, 3, 4, 17]. This is obviously an advantage for rapid control of the level of block when the drug is used by infusion and this has been shown in the present and previous studies [7, 8]. Administration of neuromuscular blocking drugs by continuous infusion provides for greater stability of drug concentrations, and ensures greater consistency in the degree of paralysis [18]. When appropriately titrated to individual patient requirements, infusion techniques have the potential to avoid periods of both inadequate and excessive drug effects [10].

The times to recovery of neuromuscular function were not unduly prolonged after the infusions. The mean recovery index of 17 min after stopping the infusion was slightly less than that reported after single bolus doses of rocuronium. This may have resulted from the fact that the patients in the present study were recovering from a level of block of 90%

maintained by infusion rather than from a complete block using a bolus dose. In the latter situation more drug is redistributed during recovery from the peripheral to the central compartment, which then tends to slow the plasma concentration decay by distribution and elimination during the recovery phase [11].

Controlled infusions titrated to effect, minimize the transfer of drug to compartments other than the effect compartment. Use of blockers in this manner, therefore, results in a faster recovery than that resulting after a similar period of block using incremental maintenance doses. However, recovery may be prolonged, with an increased recovery index, after prolonged infusions because of saturation of the distribution compartments. In this situation, distribution of the blocker from plasma to the peripheral compartments contributes progressively less and less to reduction in plasma concentrations [11]. This was not the case in the present study where the duration of infusions was relatively short.

In the present study, no metabolites were detected in plasma in any patient. Metabolites in plasma or urine in humans have been found to be either absent or below the level of detection after 0.6 or 1.0 mg kg^{-1} bolus dose administration [2, 9].

Cooper and colleagues reported values of 207 ml kg^{-1}, 3.7 ml kg^{-1} min^{-1} and 97.2 min, respectively, for steady state volume of distribution, rate of clearance and elimination half-life with 0.6 mg kg^{-1} in patients with normal renal function during isoflurane anaesthesia [9]. Values using a dose of 1 mg kg^{-1} were reported as 270 ml kg^{-1}, 4.0 ml kg^{-1} min^{-1} and 131 min, respectively [2]. In the present study, mean steady state volume of distribution and elimination half-life were 212 ml kg^{-1} and 85.6 min, respectively, after a bolus dose followed by infusion. These variables are similar to those reported by Cooper and collegues in normal patients after a bolus dose of 0.6 mg kg^{-1}, although lower than those reported by Szenohradszky and colleagues who were studying patients undergoing renal transplantation [9, 19]. The rate of clearance was also similar to that reported in the previous study of single bolus dose administration [9]. Rocuronium concentrations were 1287 ng ml^{-1} at 25% recovery of T1 and had decreased to 711 ng ml^{-1} on recovery of the TOF ratio to 0.7, which were similar to those after single bolus doses of 0.6–1.0 mg kg^{-1} [2, 9].

The use of venous samples in the present study was based on convention. Although data obtained from arterial sampling may yield different and more accurate values, in particular for V_1, in the present study we used venous sampling to allow comparison with the results obtained from the previous single dose study based on venous sampling [9].

Although patients in the present study were anaesthetized with halothane compared with isoflurane in the study of Cooper and colleagues [9] with which the results from the present study have been compared, it has been shown that there are no significant differences in the kinetics of rocuronium during anaesthesia with these two agents [20].

Studies in the cat showed that less than 10% of rocuronium was excreted in urine and, as with vecuronium, most was excreted in bile [21]. However, previous work in healthy patients and those with renal failure has suggested a considerable role for renal clearance, with approximately 30% of rocuronium being recovered unchanged from urine [2, 9]. This was associated with greater interindividual variability of effect in patients with renal disease and the possibility of a longer duration of action of rocuronium in such patients [9]. It is likely that a similar trend will be observed after the use of rocuronium by infusion.

In conclusion, the present study indicates that rocuronium is suitable for infusions of moderate duration in patients with normal hepatic and renal function, with little difference in recovery and kinetic characteristics compared with single bolus doses. The absence of detectable metabolites is in keeping with previous work with single bolus dose administration and indicates minimal metabolism even with a total dose of 1.0 mg kg^{-1}. These results, however, do not preclude possible prolonged recovery with alteration in the kinetics of the drug after a much longer period of administration or in patients with significant renal or hepatic dysfunction, or both.

Acknowledgements

Supplies of rocuronium and financial assistance were received from Organon Teknika NV, Belgium. Rocuronium assays were carried out in the Department of Experimental Pharmacology at the University of Groningen.

References

1. Foldes FF, Nagashima H, Nguyen HD, Shiller WS, Mason MM, Ohta Y. The neuromuscular effects of Org 9426 in patients receiving balanced anesthesia. *Anesthesiology* 1991; **75**: 181–196.
2. Wierda JMKH, Kleef UW, Lambalk LM, Koppenburg WD, Agoston S. The pharmacodynamics and pharmacokinetics of Org 9426, a new non-depolarizing neuromuscular blocking agent, in patients anaesthetized with nitrous oxide, halothane and fentanyl. *Canadian Journal of Anaesthesia* 1991; **38**: 430–435.
3. Cooper R, Mirakhur RK, Clarke RSJ, Boules Z. Comparison of intubating conditions after administration of Org 9426 (rocuronium) and suxamethonium. *British Journal of Anaesthesia* 1992; **69**: 269–273.
4. Cooper RA, Mirakhur RK, Maddineni VR. Neuromuscular effects of rocuronium bromide (Org 9426) during fentanyl and halothane anaesthesia. *Anaesthesia* 1993; **48**: 103–105.
5. Mirakhur RK, Ferres CJ. Muscle relaxation with an infusion of vecuronium. *European Journal of Anaesthesiology* 1986; **1**: 353–359.
6. Hunter JM, Kelly JM, Jones RS. Atracurium infusions in major ophthalmic surgery. *European Journal of Anaesthesiology* 1987; **4**: 9–15.
7. Shanks CA, Fragen RJ, Ling D. Continuous intravenous infusion of rocuronium (Org 9426) in patients receiving balanced enflurane or isoflurane anesthesia. *Anesthesiology* 1993; **78**: 649–651.
8. McCoy EP, Mirakhur RK, Maddineni VR, Loan PB, Connolly F. Administration of rocuronium (Org 9426) by continuous infusion and its reversibility with anticholinesterases. *Anaesthesia* 1994; **49**: 940–945.
9. Cooper RA, Maddineni VR, Mirakhur RK, Wierda JMKH, Brady M, Fitzpatrick KTJ. Time course and pharmacokinetics of rocuronium bromide (Org 9426) during isoflurane anaesthesia in patients with and without renal failure. *British Journal of Anaesthesia* 1993; **71**: 222–226.
10. Martineau RJ, St-Jean B, Kitts JB, Curran MC, Lindsay P, Hull KA, Miller DR. Cumulation and reversal with prolonged infusions of atracurium and vecuronium. *Canadian Journal of Anaesthesia* 1992; **39**: 670–676.

11. Wierda JMKH, Proost JH, Schiere S, Hommes FDM. Pharmacokinetics and pharmacokinetic/dynamic relationship of rocuronium bromide in humans. *European Journal of Anaesthesiology* 1994; **11** (Suppl. 9): 66–74.
12. Kleef UW, Proost JH, Roggeveld J, Wierda JMKH. Determination of rocuronium and its putative metabolites in body fluids and tissue homogenates. *Journal of Chromatography* 1993; **621**: 65–67.
13. Wagner JG. *Fundamentals of Clinical Pharmacokinetics*. Hamilton, Illinois: Drug Intelligence Publications, 1975.
14. van den Broek L, Wierda JMKH, Smeulers NJ, Proost JH. Pharmacodynamics and pharmacokinetics of an infusion of Org 9487, a new short-acting steroidal neuromuscular blocking agent. *British Journal of Anaesthesia* 1994; **73**: 331–335.
15. Press WH, Flannery BP, Teukolsky SA, Vetterling WT. *Numerical Recipes*. Cambridge: Cambridge University Press, 1986.
16. Boxenbaum HG, Riegelman S, Elashoff RM. Statistical estimations in pharmacokinetics. *Journal of Pharmacokinetics and Biopharmaceutics* 1974; **2**: 123–148.
17. Bowman WC, Rodger IW, Houston, Marshall RK, McIndewar I. Structure–action relationships among some desacetoxy analogues of pancuronium and vecuronium in the anaesthetized cat. *Anesthesiology* 1988; **69**: 57–62.
18. Shanks CA. Pharmacokinetics of the nondepolarizing neuromuscular relaxants applied to calculation of bolus and infusion dosage regimens. *Anesthesiology* 1986; **64**: 72–86.
19. Szenohradszky J, Fisher DM, Segredo V, Caldwell JE, Bragg P, Sharma ML, Gruenke LD, Miller RD. Pharmacokinetics of rocuronium bromide (Org 9426) in patients with normal renal function or patients undergoing cadaver renal transplantation. *Anesthesiology* 1992; **77**: 899–904.
20. van den Broek L, Wierda JMKH, Smeulers NJ, van Santen G-J, Leclercq GL, Hennis PJ. Clinical pharmacology of rocuronium (Org 9426): Study of the time course of action, dose requirement, reversibility and pharmacokinetics. *Journal of Clinical Anesthesia* 1994; **6**: 288–296.
21. Khuel-Brady K, Castagnoli KP, Canfell PC, Caldwell JE, Agoston S, Miller RD. The neuromuscular blocking effects and pharmacokinetics of Org 9426 and Org 9616 in the cat. *Anesthesiology* 1990; **72**: 669–674.

British Journal of Anaesthesia 1996; 76: 34–37

Effect of suxamethonium on the auditory evoked response in humans

M. D. BRUNNER, D. NATHWANI, P. A. RICH, C. THORNTON, C. J. DORÉ AND D. E. F. NEWTON

Summary

We have studied the arousal effect of suxamethonium on the auditory evoked response (AER) of the electroencephalogram (EEG) in 40 ASA I and II patients during isoflurane anaesthesia. After induction of anaesthesia, the patient's lungs were ventilated for 20 min with 0.6 MAC end-expiratory isoflurane (0.59–0.77% depending on the age of the patient), and 50% nitrous oxide in oxygen. The patients were then allocated randomly to one of two groups: 21 received suxamethonium 1 mg kg^{-1}, while 19 were given saline. The AER before and after administration of suxamethonium or saline was compared to determine the changes in Pa and Nb amplitudes and latencies. Pa amplitude after suxamethonium increased by 53% (95% confidence interval (CI) 15,104%) compared with a reduction in Pa amplitude in the saline group of 19% (95% CI, −41,12%) ($P = 0.004$) suggesting an arousal effect. Similarly, Nb amplitude increased in the suxamethonium group by 47% (95% CI, 3, 110%) and decreased in the saline group by 11% (95% CI, −33,19%) ($P = 0.03$). We conclude that suxamethonium caused arousal according to the AER and postulate that this may have been caused by increased muscle afferent activity after stimulation of muscle spindles, although further studies are required to confirm this. (*Br. J. Anaesth.* 1996; **76**: 34–37)

Key words
Neuromuscular block, suxamethonium. Brain, evoked potentials. Monitoring, evoked potentials.

The auditory evoked response (AER) has been shown to reflect levels of anaesthesia [1]. The Pa and Nb waves are early cortical components of the AER which originate in the primary auditory cortex in response to an auditory stimulus. The early cortical responses show graded changes with increasing anaesthetic concentrations for a wide range of anaesthetic drugs [2–5]. In particular, the amplitude of Pa decreases and the latency of Nb increases with increasing depth of anaesthesia, while Pa amplitude increases and Nb latency decreases during emergence from anaesthesia. When a stimulus is applied to a patient during steady state anaesthesia, for example skin incision [6] or tracheal intubation [7], Pa and Nb amplitudes increase, suggesting arousal, although no significant change has been demonstrated in Nb latency. The AER therefore reflects both level of anaesthesia and the balance between anaesthesia and stimulation. During the course of other studies in which suxamethonium was used, we observed that suxamethonium caused an arousal effect on the AER. We therefore designed a study to investigate the effects of suxamethonium on the AER.

Patients and methods

This study was approved by the Harrow Research Ethics Committee. We studied 40 ASA I and II unpremedicated patients, aged 18–65 yr. All patients gave written informed consent. Patients were excluded if they were pregnant or if ventilation of their lungs using a laryngeal mask airway (LMA) was contraindicated (hiatus hernia, oesophageal reflux).

Anaesthesia was induced with propofol 1–2 mg kg^{-1} and an LMA was inserted. The patients' lungs were ventilated with a Manley MP3 ventilator to normocapnia, measured by a Datex Capnomac Ultima. Anaesthesia was maintained with isoflurane and 50% nitrous oxide in oxygen. The end-expiratory isoflurane concentration was measured using a calibrated Datex Capnomac Ultima and was kept at 0.6 MAC, age-adjusted [8] (0.59–0.77% depending on the age of the patient), for 20 min to allow alveolar and brain concentrations of isoflurane to reach equilibrium [9]. Patients were then allocated randomly to receive either suxamethonium 1 mg kg^{-1} or saline control.

The AER was recorded from mastoid to forehead silver–silver chloride electrodes in response to a rarefaction click stimulus at 6 s^{-1}. This auditory stimulus was delivered to each ear simultaneously through close fitting ear pieces at 75 dB above the average hearing threshold. The EEG signal was analogue filtered on input with bandwidths of 25–

M. D. BRUNNER, FRCA, C. THORNTON, PHD, D. E. F. NEWTON, FRCA, Academic Department of Anaesthesia, St Mary's Hospital Medical School, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ. C. J. DORÉ, BSC, Institute of Medical Research, Statistics Department, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ. D. NATHWANI, FRCA, Department of Anaesthesia, Royal Brompton Hospital, Sydney Street, London SW3 6NP. P. A. RICH, FRCA, Department of Anaesthesia, St George's Hospital, Blackshaw Road, Tooting, London SW17 0QT. Accepted for publication: August 15, 1995.

Correspondence to M. D. B.

500 Hz to produce the AER recording which was displayed and stored continuously throughout the study on a portable computer. The AER recording continued for 2 min and 40 s after suxamethonium or saline to allow collection of 1024 sweeps of AER data. During this period, patients were left unstimulated to allow any change in AER to reflect the effect of suxamethonium or saline alone.

After each study the average of 1024 sweeps, representing 2 min and 40 s of AER data, before and after administration of suxamethonium or saline were filtered further using a high pass filter of 25 Hz and three-point smoothing. The waveforms were then printed out and analysed. Pa and Nb amplitudes and latencies were determined, and values before and after suxamethonium or saline were compared. The difference between values before (baseline) and after drug administration were calculated to show the effect of suxamethonium and saline on these AER variables.

For statistical analysis, all AER values were $\log_{10}$ transformed in order to produce homogeneity of variance and normality of residuals. A two sample *t* test was used to compare the mean change from baseline in the two groups. The difference between two logarithms is the logarithm of their ratios. When converted back to the original scale of measurement, a 95% confidence interval for the change from baseline on the logarithmic scale corresponds to a 95% confidence interval for the percentage change from baseline. The SD in the two groups for latencies were significantly different, and therefore a *t* test which does not assume equal variance was used for these values. The 95% confidence intervals for the geometric means of each group were also determined.

Results

We enrolled 44 patients into the study. Muscle artefact appears on the AER waveform in both unparalysed patients and during fasciculation in patients who have received suxamethonium. Data were included only when the underlying AER waveforms were unambiguously identifiable. On this basis data from four patients, two from each group, were excluded. Thus the results of 40 patients are presented (mean age 35.5 (range 18–63) yr; 22 females and 18 males). Twenty-one patients received suxamethonium and 19 were given saline as a control.

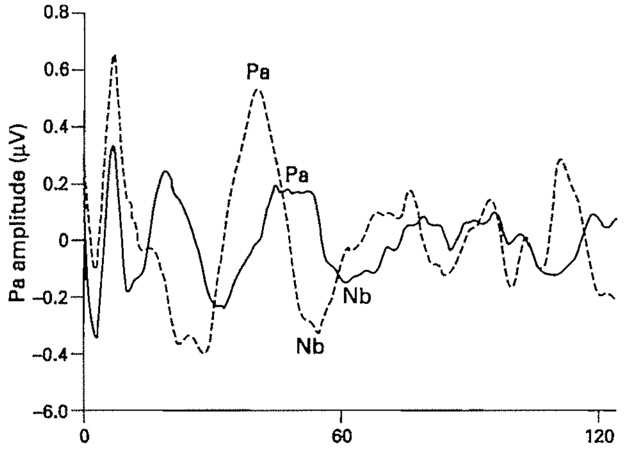


Figure 1 The auditory evoked response waveforms after an auditory click stimulus in a patient before (——) and after (——) suxamethonium. Changes in Pa and Nb amplitudes after administration of suxamethonium are illustrated.

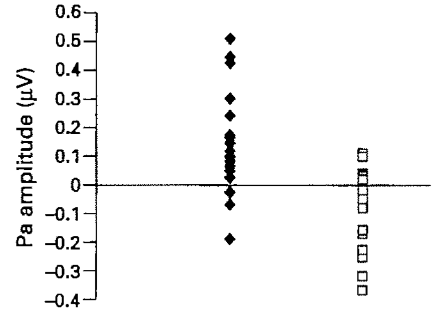


Figure 2 Change in Pa amplitude in patients after suxamethonium (◆) or saline (☐).

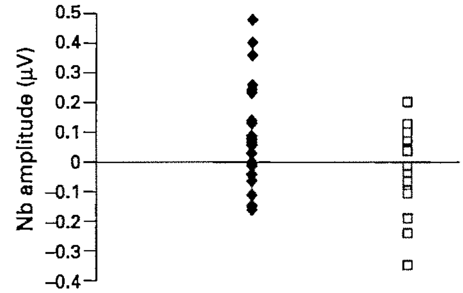


Figure 3 Change in Nb amplitude in patients after suxamethonium (◆) or saline (☐).

Typical changes in the AER waveform after suxamethonium were an increase in Pa and Nb amplitudes (fig. 1). Pa amplitude increased in 18 of 21 patients after suxamethonium and in only nine of 19 patients after saline (fig. 2). Similarly, Nb amplitude increased in 14 of 21 patients who received suxamethonium compared with eight of 19 in the saline group (fig. 3).

The percentage changes in Pa and Nb amplitudes and Pa and Nb latencies for both groups after suxamethonium or saline are shown in table 1. The mean percentage increase in Pa amplitude from baseline in the suxamethonium group was 53% (95% confidence interval (CI) 15, 104%) while in the saline group it decreased by 19% (CI −41, 12%) ($P = 0.004$) (fig. 4). Nb amplitude also increased significantly after suxamethonium compared with saline control. There were no significant differences for either Pa or Nb latencies between the two groups.

Discussion

The aim of this study was to assess the effects of suxamethonium on the AER during steady state isoflurane anaesthesia. We have shown that suxamethonium caused a significant increase in Pa and Nb amplitudes of the AER, similar to those after other stimuli, for example surgical stimulation and tracheal intubation [6, 7]. We conclude, therefore, that according to the AER suxamethonium caused arousal.

Table 1 Mean (95% confidence intervals) percentage changes in Pa and Nb amplitudes and Pa and Nb latencies from their geometric means in patients after administration of suxamethonium (Sux) ($n = 21$) or saline ($n = 19$). *P* values relate to the comparison of the percentage change from baseline in patients receiving suxamethonium or saline

AER variable	Treatment	Baseline geometric mean	% Change from baseline	*P*
Pa amplitude (μV)	Sux	0.19 (0.15, 0.23)	53 (15, 104)	0.004
	Saline	0.24 (0.17, 0.33)	−19 (−41, 12)	
Nb amplitude (μV)	Sux	0.19 (0.14, 0.26)	47 (3, 110)	0.03
	Saline	0.23 (0.18, 0.30)	−11 (−33, 19)	
Pa latency (ms)	Sux	42.4 (39.8, 45.2)	−12 (−16, −7)	0.05
	Saline	42.3 (38.9, 45.9)	−9 (−17, 1)	
Nb latency (ms)	Sux	60.8 (57.1, 64.9)	−14 (−19, −8)	0.5
	Saline	62.6 (58.7, 66.7)	−10 (−19, 1)	

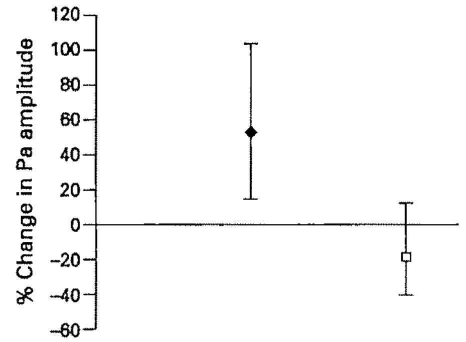


Figure 4 Mean (95% confidence intervals) percentage change from baseline in Pa amplitude for patients receiving suxamethonium (◆) or saline (□).

Previous studies have shown that suxamethonium produces an arousal pattern on the electroencephalogram (EEG) in anaesthetized humans. Mori, Iwabuchi and Fujita [10] demonstrated a change from 50–200-μV, 10–14-Hz spindle bursts to low voltage fast wave activity of 14–18 Hz. These changes occurred 60–90 s after administration of suxamethonium at a time when muscle fasciculation occurred. Oshima, Shingu and Mori [11] showed that activation of the EEG by suxamethonium was similar to that after surgical incision. This supports our findings that surgical incision and suxamethonium have similar arousal effects on the Pa and Nb amplitudes of the AER.

There are several possible causes for the arousal effects of suxamethonium. As this drug does not cross the blood–brain barrier [12] and has no effect on the EEG when injected directly into carotid arteries [13], its arousal effect on the EEG is thought to arise from its peripheral action. Muscle fasciculation caused by suxamethonium has been shown to cause arousal of the raw EEG in both humans [10, 11] and animals [13, 14]. Lanier, Milde and Michenfelder [14] showed that when dogs anaesthetized with halothane developed fasciculations after suxamethonium, there was an increase in electromyographic (EMG) activity leading to an increase in muscle spindle afferent activity, an arousal effect on the EEG and an increase in cerebral blood flow. All of these changes coincided with the duration of action of suxamethonium.

EEG arousal caused by suxamethonium, however, also occurs in the absence of fasciculation. In a later study by Lanier, Iaizzo and Milde [15], dogs anaesthetized with halothane were given a "defasciculating" dose of pancuronium (0.01 mg kg^{-1}) before administration of suxamethonium. Although this dose was insufficient to cause muscle paralysis to allow intubation, it did prevent fasciculation after suxamethonium. In these dogs, therefore, there was no change in EMG activity after suxamethonium. However, muscle spindle afferent activity increased, followed by EEG arousal and an increase in cerebral blood flow.

The arousal effect of suxamethonium on the EEG therefore, is not dependent on muscle fasciculation *per se*, but is caused by increased neuronal transmission to areas of the cortex which receive input from muscle spindles [16]. These are stimulated either indirectly as a result of extrafusal muscle fibre fasciculation, or directly by stimulation of muscle spindles themselves by suxamethonium. Suxamethonium has been shown to cause sustained contraction of intrafusal muscle fibres (muscle spindles) [17] resulting in increased muscle afferent activity [18]. This effect can be reproduced by repeated injections of suxamethonium [19] and blocked by complete neuromuscular block [20]. Indeed, a "paralysing" dose of non-depolarizing neuromuscular blocker before administration of suxamethonium has been shown to block EEG arousal after suxamethonium in humans [10] and dogs [14] anaesthetized with halothane. Increasing the depth of anaesthesia also obtunds the arousal effect of suxamethonium on the EEG [14], indicating the balance which exists between anaesthesia and stimulation. The mechanism by which suxamethonium causes arousal on the AER may be similar to that postulated for its arousal effects on the EEG. However, further studies on the effect of suxamethonium on the AER after pretreatment with a defasciculating or paralysing dose of a non-depolarizing neuromuscular blocker are needed to define the mechanism by which suxamethonium causes AER arousal.

Anecdotal evidence suggests that reports of awareness or arousal in anaesthetized patients are more common at, or around the time of tracheal intubation. This may be explained by the fact that two stimuli, administration of suxamethonium and tracheal intubation, both of which cause arousal according to the AER, occur almost simultaneously. The arousal effect of suxamethonium has been demonstrated in the clinical setting by Hobbs, Bush and Downham [21], in a study on paediatric patients anaesthetized with a nitrous oxide–oxygen–neuromuscular blocker technique. This study showed that the incidence of dreaming was increased ($P < 0.05$) if intermittent suxamethonium was chosen as the neuromuscular blocker (24%) compared with atracurium (9%). Minton and colleagues [22] showed, in a within-patient study, that intracranial pressure (ICP) in patients with brain tumours increased after suxamethonium, whereas this increase was blocked if suxamethonium was given after a paralysing dose of vecuronium. The authors concluded that the increase in ICP in their patients after suxamethonium alone resulted from an increase in cerebral blood flow produced by EEG arousal caused by stimulation of muscle spindles.

We postulate, therefore, that the increases in Pa and Nb amplitudes which we have described after suxamethonium, may result from cerebral arousal caused by increased muscle spindle afferent activity. The role of extrafusal muscle fasciculation in this phenomenon cannot be determined because our study was not designed to distinguish between the direct and indirect effects of suxamethonium on muscle spindles.

References

1. Thornton C. Evoked potentials in anaesthesia. *European Journal of Anaesthesiology* 1991; **8**: 89–107.
2. Thornton C, Heneghan CPH, Navaratnarajah M, Bateman PE, Jones JG. Effect of etomidate on the auditory evoked response in man. *British Journal of Anaesthesia* 1985; **57**: 554–561.
3. Heneghan CPH, Thornton C, Navaratnarajah M, Jones JG. Effect of isoflurane on the auditory evoked response in man. *British Journal of Anaesthesia* 1987; **59**: 277–282.
4. Thornton C, Konieczko K, Knight AB, Kaul B, Jones JG, Doré CJ, White DC. Effect of propofol on the auditory evoked response and oesophageal contractility. *British Journal of Anaesthesia* 1989; **63**: 411–417.
5. Thornton C, Heneghan CPH, James MFM, Jones JG. Effects of halothane or enflurane with controlled ventilation on auditory evoked potentials. *British Journal of Anaesthesia* 1984; **56**: 315–323.
6. Thornton C, Konieczko K, Jones JG, Doré CJ, Heneghan CPH. Effect of surgical stimulation on the auditory evoked response. *British Journal of Anaesthesia* 1988; **60**: 372–378.
7. Thornton C, Creagh-Barry P, Jordan C, Newton DEF. Anaesthetic depth and auditory evoked potentials. *Acta Anaesthesiologica Scandinavica* 1993; **37** (Suppl. 100): 105–108.
8. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI II, Miller RD, DeJong RH, Elashoff RM. Minimum alveolar concentrations, MAC of isoflurane with and without nitrous oxide in patients of various ages. *Anaesthesiology* 1975; **42**: 197–200.
9. Quasha AL, Eger IE, Tinker JH. Determination and application of MAC. *Anaesthesiology* 1980; **53**: 315–334.
10. Mori K, Iwabuchi K, Fujita M. The effects of depolarizing muscle relaxants on the electroencephalogram and the circulation during halothane anaesthesia in man. *British Journal of Anaesthesia* 1973; **45**: 604–610.
11. Oshima E, Shingu K, Mori K. E.E.G. activity during halothane anaesthesia in man. *British Journal of Anaesthesia* 1981; **53**: 65–72.
12. Dal Santo G. Kinetics of distribution of radioactive labeled muscle relaxants: III. Investigations with ^{14}C-succinyldicholine and ^{14}C-succinylmonocholine during controlled conditions. *Anaesthesiology* 1968; **29**: 435–443.
13. Motokizawa F, Fujimori B. Arousal effect of afferent discharges from muscle spindles upon electroencephalograms in cats. *Japanese Journal of Physiology* 1964; **14**: 344–353.
14. Lanier WL, Milde JH, Michenfelder JD. Cerebral stimulation following succinylcholine in dogs. *Anaesthesiology* 1986; **64**: 551–559.
15. Lanier WL, Iaizzo PA, Milde JH. Cerebral function and muscle afferent activity following intravenous succinylcholine in dogs anesthetized with halothane: The effects of pretreatment with a defasciculating dose of pancuronium. *Anaesthesiology* 1989; **71**: 87–95.
16. Giaquinto S, Pompeiano O, Sweet JE. EEG and behavioural effects of fore- and hindlimb muscular afferent volleys in unrestrained cats. *Archives Italiennes de Biologie* 1963; **101**: 133.
17. Smith CM, Eldrid E. Mode of action of succinylcholine on sensory endings of mammalian muscle spindles. *Journal of Pharmacology and Experimental Therapeutics* 1961; **131**: 237–242.
18. Satoyoshi M, Muto K, Shimazu H, Sakai Y. Effects of ether and succinylcholine on cat spinal reflex. *Japanese Journal of Anesthesia* 1961; **10**: 531.
19. Brinling JC, Smith CM. A characterization of the stimulation of mammalian muscle spindles by succinylcholine. *Journal of Pharmacology and Experimental Therapeutics* 1960; **129**: 56–60.
20. Granit R, Skoglund S, Thesleff S. Activation of muscle spindles by succinylcholine and decamethonium. The effects of curare. *Acta Physiologica Scandinavica* 1953; **28**: 134–151
21. Hobbs AJ, Bush GH, Downham DY. Peri-operative dreaming and awareness in children. *Anaesthesia* 1988; **43**: 560–562.
22. Minton MD, Grosslight K, Stirt JA, Bedford RF. Increases in intracranial pressure from succinylcholine: Prevention by prior nondepolarizing blockade. *Anesthesiology* 1986; **55**: 165–169.

British Journal of Anaesthesia 1996; **76**: 38–42

Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by evoked potentials

D. ROTH, S. PETERSEN-FELIX, P. BAK, L. ARENDT-NIELSEN, M. FISCHER, P. BJERRING AND A. M. ZBINDEN

Summary

The aim of this study was to see if an analgesic effect of subanaesthetic concentrations of isoflurane could be detected with evoked potentials elicited by nociceptive stimuli. We studied 10 healthy volunteers breathing three steady-state subanaesthetic concentrations of isoflurane (0.08, 0.16 and 0.24 vol% end-tidal). Reaction time, subjective pain intensities and evoked vertex potentials to laser (LEP) and electrical (SEP) stimuli were recorded and compared with auditory evoked potentials (AEP). Compared with baseline, the subanaesthetic concentrations of isoflurane did not change the latencies of the evoked potentials, but caused a significant reduction in the amplitudes of the LEP and SEP at 0.16 and 0.24 vol% and of the AEP at all three concentrations. There were no changes in perceived pain intensity, and isoflurane produced similar reductions in evoked potentials elicited by both nociceptive and non-nociceptive stimuli. The reaction time was increased significantly at 0.24 vol% isoflurane. The results demonstrated that subanaesthetic isoflurane concentrations caused similar changes in evoked potentials with both painful and non-painful stimuli, with no effect on perceived pain intensity. (*Br. J. Anaesth.* 1996; **76**: 38–42)

Key words

Anaesthetics volatile, isoflurane. Pain, experimental. Monitoring, evoked potentials.

The analgesic effect of subanaesthetic concentrations of inhalation anaesthetics has been investigated by either clinical assessment [1–3] or pain threshold measurements [4, 5], but with conflicting results. In a recent study we found no analgesic effect of subanaesthetic concentrations of isoflurane on experimental pain tests [6]. These pain tests may, however, not always be able to detect a weak analgesic effect [7]. Laser stimulation may be a more sensitive method, as this has been used to demonstrate the analgesic effect of weak analgesics [8–11]. The purpose of the present study therefore was to see if evoked vertex potentials elicited by nociceptive electrical and laser stimulation could be used to detect weak analgesic effects of subanaesthetic concentrations of isoflurane.

Patients and methods

We studied 10 healthy volunteers (five male, mean age 24 (range 22–30) yr). They were not receiving any medication, had no allergies or adverse reactions to previous anaesthetics and, for the female volunteers, were not pregnant. Written informed consent was obtained and the study was approved by the Ethics Committee of the Faculty of Medicine, University of Bern.

To minimize the risk of acid aspiration, the volunteers received omeprazole 40 mg (Antra) the evening before testing, and were investigated after a fasting period of at least 6 h. During the tests the volunteers rested comfortably supine. An i.v. infusion of NaCl–glucose was given and Sp_{O_2}, ECG and non-invasive arterial pressure were monitored continuously. The subanaesthetic concentrations of isoflurane were delivered via a face mask. The breathing system and the gas monitors have been described previously [6].

The following tests were applied in a randomized order.

ARGON LASER STIMULATION

The output from an argon laser (Spectra Physics 168) was transmitted via a single 0.2-mm quartz fibre (output controlled with an external power meter). The distance to the skin was adjusted to obtain a laser beam diameter of 3 mm on the skin and a stimulus of 200 ms duration was applied to the dorsum of the right hand (C7 dermatome). The target area was divided into small sectors and, to avoid receptor fatigue, the sectors were stimulated sequentially. Pain threshold, defined as a distinct sharp pinprick, was determined with five ascending and five descending series of stimulation. For

---

DANIEL ROTH, STEEN PETERSEN-FELIX, MD, DEAA, MICHAEL FISCHER, MD, ALEX M. ZBINDEN, MD, PHD, Department of Anaesthesiology and Intensive Care, University Hospital of Bern, Switzerland. PETER BAK, MSC, EE, LARS ARENDT-NIELSEN, PHD, Centre for Sensory–Motor Interaction, University of Aalborg, Denmark. PETER BJERRING, MD, PHD, Department of Dermatology, University Hospital of Aarhus, Denmark. Accepted for publication: August 14, 1995.

*Address for correspondence: Institut für Anästhesie und Intensivbehandlung, Inselspital, CH-3010 Bern, Switzerland.

recording of the laser evoked potentials (LEP), 16 laser stimuli with an intensity of 1.5 times the initial pain threshold and with a random inter-stimulus interval between 10 and 20 s were applied. After the last stimulation, the volunteer was asked to rate the perceived pain intensity on a visual analogue scale (VAS).

ELECTRICAL STIMULATION

An intracutaneous finger electrode applied to the pulp of the third finger was used [12]. A 25-ms single stimulus (in reality train of five, 1-ms, square-wave impulses, but these are perceived as a single stimulus) was delivered from a Digitimer DS 7 (Digitimer Ltd, Hertfordshire, England) constant current stimulator triggered by a Philips Generator PM 5150 (Philips GmbH, Hamburg, Germany). The current was increased from 0 in steps of 0.2 mA until the volunteer rated the perceived pain intensity of the stimulation on the VAS equally with that of laser stimulation. This intensity was then used for recording of the SEP. Application of the 16 stimuli and rating of perceived pain intensity were performed as for the LEP.

ACOUSTICAL STIMULATION

A binaural click with an intensity of 90 dB was provided by a Medelec ST 10 stimulator (Medelec Ltd, Surrey, England) through acoustically shielded headphones. For recording of the AEP, 16 stimuli with a random inter-stimulus interval between 10 and 20 s were applied as described for the laser and electrically evoked vertex potentials.

REACTION TIME

A tone was delivered from a computer with random intervals of 3–8 s, and simultaneously a timer was started. The volunteer was told to press a button as fast as possible after the tone. The reaction time was defined as the time from the tone until the volunteer pressed the button. The mean value of three consecutive measurements was used.

RECORDING OF THE EVOKED POTENTIALS

All evoked potentials were recorded from a needle electrode (Dantec, Denmark), inserted at Cz′ (according to the international 10–20 system) against a surface Ag–AgCl electrode on the right mastoid. The signal was filtered (bypass 0.1–30 Hz), amplified, recorded and averaged on a personal computer (PC) with the EPsys software (Aalborg University, Denmark) in the interval from 0.5 s before the stimulus until 2 s after the stimulus.

In order to familiarize the volunteer with the procedure, all experiments were explained before trial testing was performed. The mask was then fitted and the volunteer breathed air for 5 min, or until he felt comfortable, and there were no leaks from the mask. A baseline test series of the above described tests was then performed. Thereafter, isoflurane was introduced slowly into the breathing system and adjusted to the desired end-tidal concentration. This was chosen randomly from one of the three concentrations, 0.08, 0.16 and 0.24 vol%. We did not use concentrations higher than 0.24 vol% (about 0.2 MAC isoflurane), as volunteers at higher concentrations tend to be too sedated to co-operate [13]. After 15 min of equilibration at a constant end-tidal concentration, a test series was performed. This procedure was repeated with the two other isoflurane concentrations. The delivered isoflurane concentration was known only to the anaesthetist performing "anaesthesia". After testing had been performed at all three isoflurane concentrations, isoflurane was discontinued.

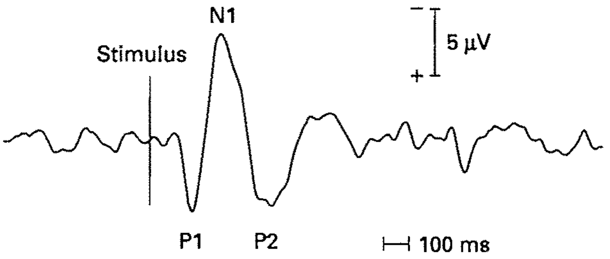


Figure 1 An LEP, which is the average of 16 evoked potentials elicited by short laser stimulations of 200 ms duration.

Latencies and peak-to-peak amplitudes of the first three major peaks, P1, N1 and P2 of the late LEP, SEP and AEP were measured (fig. 1). Statistical analysis was performed independently for each class of the evoked vertex potentials and the reaction time with the software SigmaStat v1.01 (Jandel Scientific GmbH, Erkrath, Germany). Median values and quartiles were calculated for the three isoflurane concentrations. The numerical values of all measurements were expressed as a percentage of baseline values. The values at the different isoflurane concentrations were compared with baseline using Friedman's test for repeated measures analysis of variance on ranks, and the Student–Newman–Keuls test for multiple comparison. $P < 0.05$ was considered statistically significant.

Results

Evoked vertex potentials were recorded in all subjects. There were no statistically significant changes in the latencies of the LEP and SEP compared with baseline (table 1) or with the AEP. The results in the peak-to-peak amplitudes are summarized in table 2. Statistically significant reductions compared with baseline were observed for P1–N1 amplitudes of the SEP at 0.16 and 0.24 vol% and for AEP at 0.08, 0.16 and 0.24 vol% isoflurane. N1–P2 amplitudes were reduced significantly for the LEP and SEP at 0.16 and 0.24 vol% and for AEP at 0.08, 0.16 and 0.24 vol% isoflurane. Furthermore, N1–P2 amplitude of the SEP at 0.08 vol% was reduced significantly less compared with those of the SEP and AEP at 0.16 and 0.24 vol%. There were no

Table 1 Change in latencies (median (25–75 percentiles)) of evoked vertex potentials to laser, electrical and auditory stimulation. Values are percentage of baseline values

Latencies	Isoflurane 0.08%	 0.16%	 0.24%
Laser evoked potentials P1	102.9 (100.0–108.8)	99.0 (95.9–103.1)	103.3 (98.1–115.1)
Laser evoked potentials N1	99.3 (96.1–102.5)	99.2 (97.4–102.5)	101.0 (95.1–114.5)
Laser evoked potentials P2	97.6 (94.8–100.0)	98.3 (95.8–101.4)	94.4 (85.3–101.9)
Somatosensory evoked potentials P1	106.3 (76.5–109.3)	102.0 (94.9–116.0)	113.6 (100.0–122.9)
Somatosensory evoked potentials N1	97.6 (93.2–100.0)	102.2 (100.0–107.1)	98.6 (91.4–109.3)
Somatosensory evoked potentials P2	102.7 (96.1–104.7)	99.7 (90.7–105.4)	101.4 (95.9–104.7)
Auditory evoked potentials P1	100.0 (95.6–100.0)	100.0 (100.0–105.1)	106.9 (100.0–110.3)
Auditory evoked potentials N1	101.5 (100.0–106.0)	100.0 (95.3–108.0)	108.4 (103.2–114.3)
Auditory evoked potentials P2	95.4 (93.1–101.9)	102.3 (93.1–107.6)	96.7 (90.7–107.6)

Table 2 Change in amplitudes (median (25–75 percentiles)) of evoked vertex potentials to laser, electrical and auditory stimulation. Values are percentage of baseline values. *$P < 0.05$ compared with baseline; †$P < 0.05$ compared with baseline and the SEP at 0.08 vol% isoflurane

Amplitudes	Isoflurane 0.08%	 0.16%	 0.24%
Laser evoked potentials P1–N1	98.5 (51.6–126.9)	64.7 (54.4–86.6)	51.8 (30.4–107.1)
Laser evoked potentials N1–P2	76.2 (51.7–100.0)	68.9 (23.6–83.8)*	47.2 (37.5–55.8)*
Laser evoked potentials VAS	97.4 (89.7–100.0)	98.5 (90.0–105.3)	103.7 (92.0–108.7)
Somatosensory evoked potentials P1–N1	49.6 (42.0–86.0)	50.9 (28.9–61.9)*	18.3 (6.8–42.1)*
Somatosensory evoked potentials N1–P2	76.5 (59.5–102.7)	51.5 (35.8–59.4)†	40.9 (17.9–60.7)†
Somatosensory evoked potentials VAS	90.0 (66.7–100.0)	88.6 (71.2–111.1)	87.0 (65.9–111.1)
Auditory evoked potentials P1–N1	53.8 (37.7–65.7)*	48.0 (39.7–54.6)*	45.8 (36.1–70.7)*
Auditory evoked potentials N1–P2	56.1 (40.8–67.5)*	39.0 (37.1–51.6)†	42.3 (25.0–58.9)†

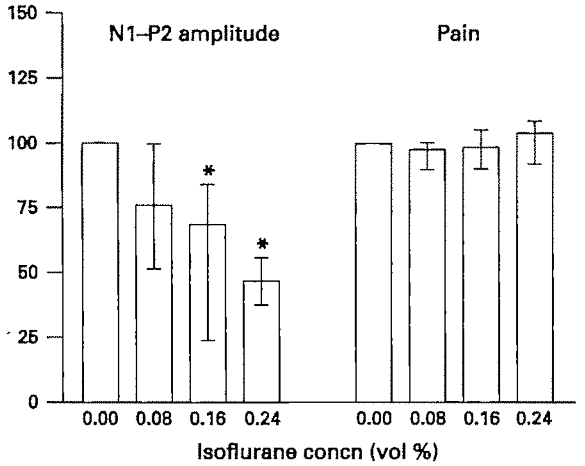


Figure 2 Argon laser stimulation. Comparison between the decrease in N1–P2 amplitude (expressed as percentage of baseline values) with increasing isoflurane concentrations of the long latency vertex potential to laser stimuli, and the perceived pain rated on a visual analogue scale. *Significantly different from baseline.

significant differences between the reductions in the amplitudes of the LEP and SEP compared with the AEP at each of the three isoflurane concentrations (figs 2–4).

There was no significant reduction in perceived pain intensity for either laser or electrical stimulation. Compared with baseline, median reaction time was 97.7% (25–75 percentiles 79.7–127.9%) at 0.08 vol%, 116.5% (94.2–128.7%) at 0.16 vol% and 161.1% (131.6–238.7%) at 0.24 vol%. Reaction time was increased significantly at 0.24 vol% compared with baseline, 0.08 and 0.16 vol%.

Discussion

We have shown that subanaesthetic concentrations of isoflurane did not change the latencies of the evoked vertex potentials, but caused a significant reduction in the amplitudes of the LEP and SEP at 0.16 and 0.24 vol% and of the AEP at all three concentrations. There was no change in perceived pain intensity, and isoflurane produced similar

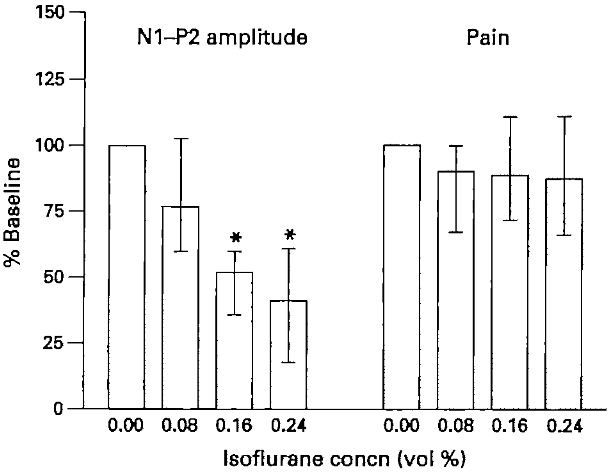


Figure 3 Electrical stimulation. Comparison between the decrease in N1–P2 amplitude (expressed as percentage of baseline values) with increasing isoflurane concentrations of the long latency vertex potential to electrical stimuli, and the perceived pain rated on a visual analogue scale. *Significantly different from baseline.

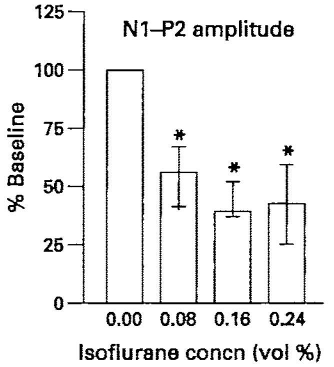


Figure 4 Auditory stimulation. Decrease in N1–P2 amplitude (expressed as percentage of baseline values) with increasing isoflurane concentrations of the long latency vertex potential to auditory stimuli. *Significantly different from baseline.

reductions in amplitudes of the evoked potentials elicited by both nociceptive and non-nociceptive stimuli. The reaction time was increased significantly at 0.24 vol% isoflurane. We conclude that subanaesthetic concentrations of isoflurane have a sedative but no or only a minimal analgesic effect which the present techniques could not detect.

Several studies have shown that potentials, evoked by noxious laser stimuli, correlate with perceived pain intensity [10, 11, 14, 15]. In contrast, there is a lack of correlation between the amplitude of the vertex potential evoked by nociceptive electrical stimulation on the surface of the skin and subjective pain rating [16, 17]. This suggests that transcutaneous electrically evoked vertex potentials are not a reliable measure or correlate for changes within the nociceptive system.

In the present study electrical stimulation was applied using the intracutaneous technique [12]. This procedure ensured a high current density at the superficial nociceptors. As a consequence, pain thresholds were up to 10 times lower compared with transcutaneous stimulation. The sensation is described as a distinct pricking pain, very similar to that elicited by laser stimulation. This perception is attributed to the activity in the Aδ nociceptive afferents [18]. Kochs and colleagues [19] used the same technique for eliciting late SEP. They found that the recorded SEP were sensitive to opioid treatment during inhalation anaesthesia.

We did not find any correlation between the decrease in amplitudes of the LEP and SEP, and subjective pain rating. There was a reduction in the peak-to-peak amplitudes for the evoked vertex potentials elicited by nociceptive electrical and laser stimulation at the two higher isoflurane concentrations (see table 2), which could be interpreted as an analgesic effect [16, 20–22]. But the same decrease in the peak-to-peak amplitudes was observed also for the non-nociceptive AEP, and furthermore the perceived pain intensity did not differ significantly from baseline. These results suggest that the reduction in peak-to-peak amplitudes of the LEP and SEP are caused by a non-specific effect of isoflurane on the vertex potentials (sedation?) rather than by a specific analgesic effect on the nociceptive system.

We have shown that when evoked vertex potentials are used to investigate the analgesic effect of a drug, it is important not only to evaluate the effects of nociceptive stimuli, but also to control for a non-analgesic general effect on the evoked vertex potentials elicited by non-nociceptive stimuli. Furthermore, the electrophysiological responses should (when possible) be compared with subjective pain ratings. If we had measured only the effect of subanaesthetic concentrations of isoflurane on the amplitude of the evoked vertex potentials to painful laser and electrical stimulation, we would have presumed this to result from an analgesic effect, which in reality was not present.

Acknowledgement

The study was supported by the Danish Basic Research Foundation, The Desireé and Niels Yde Foundation. The authors thank the Anaesthesia Research Department for technical assistance, especially D. Leibundgut.

References

1. Major V, Rosen M, Mushin WW. Methoxyflurane as an obstetric analgesic: a comparison with trichloroethylene. *British Medical Journal* 1966; **2**: 1554–1561.
2. Abboud TK, Gangolly J, Mosaad P, Crowell D. Isoflurane in obstetrics. *Anesthesia and Analgesia* 1989; **68**: 388–391.
3. McLeod DD, Ramayya GP, Tunstall ME. Self-administered isoflurane in labour. *Anaesthesia* 1985; **40**: 424–426.
4. Siker ES, Wolfson B, Ciccarelli HE, Telan RA. Effect of subanesthetic concentrations of halothane and methoxyflurane on pain threshold in conscious volunteers. *Anesthesiology* 1967; **28**: 337–342.
5. Tomi K, Mashimo T, Tashiro C, Yagi M, Pak M, Nishimura S, Nishimura M, Yoshiya I. Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans. *British Journal of Anaesthesia* 1993; **70**: 684–686.
6. Petersen-Felix S, Arendt-Nielsen L, Bak P, Roth D, Fischer M, Bjerring P, Zbinden AM. Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by experimentally induced pain. *British Journal of Anaesthesia* 1995; **75**: 55–60.
7. Jones SF, McQuay HJ, Moore RA, Hand CW. Morphine and ibuprofen compared using the cold pressor test. *Pain* 1988; **34**: 117–122.
8. Arendt-Nielsen L, Bjerring P. Laser-induced pain for

evaluation of local analgesia: A comparison of topical application (EMLA) and local injection (lidocaine). *Anesthesia and Analgesia* 1988; **67**: 115–123.

9. Arendt-Nielsen L, Øberg B, Bjerring P. Analgesic efficacy of i.m. alfentanil. *British Journal of Anaesthesia* 1990; **65**: 164–168.
10. Nielsen JC, Bjerring P, Arendt-Nielsen L, Petterson KJ. A double-blind, placebo controlled, cross-over comparison of the analgesic effect of ibuprofen 400 mg and 800 mg on laser-induced pain. *British Journal of Clinical Pharmacology* 1990; **30**: 711–715.
11. Nielsen JC, Bjerring P, Arendt-Nielsen L, Petterson KJ. Analgesic efficacy of immediate and sustained release paracetamol and plasma concentrations of paracetamol. Double blind, placebo-controlled evaluation using painful laser stimulation. *European Journal of Clinical Pharmacology* 1992; **42**: 261–264.
12. Bromm B, Meier W. The intracutaneous stimulus: a new pain model for algesimetric studies. *Methods and Findings in Experimental Clinical Pharmacology* 1984; **6**: 405–410.
13. Newton DEF, Thornton C, Konieczko K, Frith CD, Doré CJ, Webster NR, Luff, NP. Levels of consciousness in volunteers breathing sub-MAC concentrations of isoflurane. *British Journal of Anaesthesia* 1990; **65**: 609–615.
14. Svensson P, Arendt-Nielsen L, Kaaber S, Bjerring P. Vertex potentials evoked by nociceptive laser stimulation of oral mucosa: Relationship to stimulus intensity. *Anaesthesia and Pain Control in Dentistry* 1993; **2**: 27–33.
15. Arendt-Nielsen L. First pain related evoked potentials to argon laser stimuli: recording and quantification. *Journal of Neurology, Neurosurgery and Psychiatry* 1990; **53**: 398–404.
16. Hill H, Walter MH, Saeger L, Sargur M, Sizemore W, Chapman CR. Dose effects of alfentanil in human analgesia. *Clinical Pharmacology and Therapeutics* 1986; **40**: 178–186.
17. Brennum J, Jensen TS. Relationship between vertex potentials and magnitude of pre-pain and pain sensations evoked by electrical skin stimuli. *Electroencephalography and Clinical Neurophysiology* 1992; **85**: 387–390.
18. Torebjörk HE, Ochoa JL. Specific sensations evoked by activity in single identified sensory units in man. *Acta Physiologica Scandinavica* 1980; **110**: 445–447.
19. Kochs E, Treede R-D, Schulte am Esch J, Bromm B. Modulation of pain-related somatosensory evoked potentials by general anesthesia. *Anesthesia and Analgesia* 1990; **71**: 225–230.
20. Treede R-D, Kief S, Hölzer T, Broom B. Late somatosensory evoked cerebral potentials in response to cutaneous heat stimuli. *Electroencephalography and Clinical Neurophysiology* 1988; **70**: 429–441.
21. Arendt-Nielsen L, Øberg B, Bjerring P. Quantitative assessment of extradural bupivacaine analgesia. *British Journal of Anaesthesia* 1990; **65**: 633–638.
22. Arendt-Nielsen L, Gotliebsen K. Segmental inhibition of laser-evoked brain potentials by ipsi- and contralaterally applied cold pressor pain. *European Journal of Applied Physiology* 1992; **64**: 56–61.

British Journal of Anaesthesia 1996; **76**: 43–48

Use of near infrared spectroscopy to estimate cerebral blood flow in conscious and anaesthetized adult subjects

H. OWEN-REECE, C. E. ELWELL, W. HARKNESS, J. GOLDSTONE, D. T. DELPY, J. S. WYATT AND M. SMITH

Summary

Near infrared spectroscopy (NIRS) can be used to quantify cerebral haemodynamic states non-invasively and to estimate cerebral blood flow (CBF). In the first part of this study we have compared CBF measurements in conscious and anaesthetized subjects. In the second part we have compared paired measurements made during anaesthesia, first on the scalp and then the dura after craniotomy. Mean CBF was 17 (SD 7) ml 100 g^{-1} min^{-1} in the conscious subjects compared with 21 (8) ml 100 g^{-1} min^{-1} on the scalp during anaesthesia ($P > 0.1$). Mean CBF on the dura was 68 (21) ml 100 g^{-1} min^{-1} ($P < 0.0001$). Computer modelling suggests that the difference in magnitude between scalp and dura measurements of CBF is likely to be caused by the optical effect of extracerebral tissue which powerfully scatters light passing through it but does not contribute significantly to the measured CBF because it has only a small blood content itself. The results lend support to this method of estimating CBF although formal validation by comparison with an established technique is needed. (*Br. J. Anaesth.* 1996; **76**: 43–48)

Key words

Brain, blood flow. Measurement techniques, near infrared spectroscopy.

Although the assessment of cerebral perfusion is of great clinical importance, the measurement techniques that are currently available have notable drawbacks. Some use ionizing radiation and others require cannulation of the large cerebral vessels. Doppler velocimetry is non-invasive but measures cerebral blood flow velocity and not cerebral blood flow (CBF) directly; furthermore, it is affected by changes in the diameter of the insonated vessel and the angle of insonation.

Near infrared spectroscopy (NIRS) is a non-invasive technique which is capable of measuring changes in the concentration of tissue oxy- and deoxyhaemoglobin (HbO_2 and Hb) [1, 2]. If optical fibre bundles are applied to the scalp, measurements can be obtained from the intact head. Several variables may be measured, including cerebral blood volume (CBV) [3], cerebral blood flow (CBF) [4] and the response of the cerebral circulation to alterations in Pa_{CO_2} [5]. The technique for measuring CBF was described initially using a bolus of HbO_2 generated in the lungs as a marker of brain-blood inflow but a modification using indocyanine green has been developed recently [6]. The HbO_2 method has been validated in newborn infants [7, 8]. The method has also been used to measure CBF [9] and forearm muscle blood flow in adults [10].

The aim of the first part of the study was to apply this technique using optical fibres placed on the scalp as described previously [9] in order to compare measurements of CBF in conscious adult volunteers with those made in patients undergoing general anaesthesia. The second part of the study, in patients undergoing craniotomy, compared measurements of CBF obtained when the optical fibres were placed on the scalp with measurements obtained using fibres placed directly on the dura.

Methods and materials

SUBJECTS

Conscious subjects

Eleven healthy volunteers with a mean age of 30 (range 21 to 44) yr gave informed consent. The subjects lay supine with eyes closed, breathing a gas mixture of oxygen and nitrogen from a modified anaesthetic machine using a mouthpiece and nose occluder. Fractional inspired oxygen concentration ($F_{I_{O_2}}$) (model 5550, Hudson, CA, USA), end-tidal carbon dioxide concentration (Datex Cardiocap, Datex Inc., Helsinki, Finland) or transcutaneous carbon dioxide concentration (Novametrix 850, Novametrix Inc., Wallingford, CT, USA), were monitored. Arterial oxygen saturation (Sp_{O_2}) was measured on the earlobe with a pulse oximeter

---

H. OWEN-REECE, BSC, FRCA, J. GOLDSTONE, MD, FRCA, Department of Anaesthesia, UCL Hospitals, Middlesex Hospital, Mortimer Street, London W1N 8AA. C. E. ELWELL, PHD, D. T. DELPY, DSC, Department of Medical Physics and Bioengineering, University College London, Shropshire House, Capper Street, London WC1E 6JA. W. HARKNESS, FRCS (Department of Neurological Surgery), M. SMITH, FRCA (Department of Anaesthesia), The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG. J. S. WYATT, BSC, FRCP, Department of Paediatrics, University College London Medical School, Rayne Institute, University Street, London WC1E 6JJ.

Accepted for publication: July 29, 1995.

modified to update the value with every heartbeat (Nellcor N200E, Nellcor, Hayward, CA, USA). Heart rate was recorded from the pulse oximeter. The subject's haemoglobin concentration was estimated from a sample of blood.

Anaesthetized subjects

Ten anaesthetized patients were studied during neurosurgery for medically intractable epilepsy. Their mean age was 32 (range 19 to 48) yr. The neuropathological diagnosis in nine was hippocampal sclerosis. The remaining subject had a dysembryoplastic neuroepithelial tumour. The patients were otherwise healthy. Anaesthesia was induced with fentanyl 100 µg and thiopentone 3–6 mg kg^{-1} i.v. and maintained with isoflurane up to 1.1 % in 30–35 % oxygen with nitrous oxide. Vecuronium 0.1 mg kg^{-1} was used to provide neuromuscular block for tracheal intubation and paralysis was subsequently maintained with an infusion of the same drug. In addition to routine clinical monitoring end-tidal carbon dioxide and end-tidal isoflurane concentration (Datex Capnomac) were measured throughout the procedure. End-tidal isoflurane concentration was kept constant during CBF measurements. The lungs were ventilated to normocapnia. Mean arterial pressure (MAP) was measured either oscillometrically or by transduction from a radial arterial cannula. Incremental doses of fentanyl and labetalol were given to keep MAP as constant as possible throughout the studies. Sp_{O_2} was measured on the earlobe. Body temperature was not measured as all measurements were made close to the start of anaesthesia and normal warming techniques were employed. Near infrared spectroscopy measurements were obtained from the scalp in all 10 subjects and from the dura in seven subjects.

NEAR INFRARED SPECTROSCOPY (NIRS)

A portable NIRS apparatus (NIRO 500 or 1000, Hamamatsu Photonics KK, Hamamatsu, Japan) was used. Near infrared light at four (NIRO 500) or six (NIRO 1000) wavelengths between 700 and 910 nm was conveyed by a fibreoptic cable to the subject's head. A similar fibre bundle conveyed light transmitted through the head back to the apparatus. The end of the fibre (optode) was positioned on the left frontal region of the scalp avoiding the temporalis muscle. The median distance between the optodes was 4.2 (range 3.4–5.3) cm on the scalp. The optodes were covered with an opaque cloth to prevent interference from background illumination.

When measurements were made on the dura the optical fibres were sealed in sterile plastic film ('Steridrape', 3M) and held gently in position on the temporal dura using a Yasargil clamp (Down's Aesculap, London, UK). The interoptode distance was 2.5 cm.

Changes in light absorption were detected and converted into changes in the intracranial concentrations of HbO_2 and Hb using a previously established algorithm [11, 12]. This makes use of the Lambert-Beer relationship modified to take account of the increase in optical pathlength because of intense light scattering by biological tissue. A pathlength factor of 5.9 times the distance between the optical fibres was assumed [13]. Changes in total cerebral haemoglobin concentration (Hbsum) were calculated from the sum of the changes in HbO_2 and Hb concentrations. The details of these calculations have been described elsewhere [14].

Measurements were made continuously with a sampling interval of 0.5 s and displayed on a computer screen during the study. The NIRS, Sp_{O_2} and end-tidal carbon dioxide data were recorded simultaneously onto a computer disk for analysis later. All measurements were made under steady-state conditions.

The studies were approved both by the Joint Committee on the Ethics of Medical Investigation of University College London Hospitals and by the Joint Medical Ethics Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology. Informed written consent was obtained before each study.

CBF MEASUREMENTS

CBF was estimated using a modification of the Fick principle according to a previously established technique [4, 9]. A transient increase in Fi_{O_2} produced a bolus of HbO_2 which acted as an intravascular tracer; it was measured in the arterial system by pulse oximetry and its entry into the brain was detected by NIRS.

Before each measurement of CBF the Fi_{O_2} was reduced to allow Sp_{O_2} to equilibrate at 91–93 % for 10–20 s. Three to four breaths of 100 % oxygen were then given, causing Sp_{O_2} to increase rapidly to 97–98 % in less than 10 s. The change in cerebral HbO_2 concentration was determined by the NIRS apparatus. The first 4 s of tracer wash-in were taken for each estimation of CBF, on the basis of evidence that mean cerebral transit time is between 6 and 10 s [15]. After re-establishment of a stable baseline a mean of 4 usable measurements were obtained in each subject. The mean value for CBF was then calculated for each subject using the formula:

$$\mathrm{CBF} = \mathrm{K}\frac{\Delta \mathrm{HbO_2}}{\int_0^t \Delta f Sp_{O_2}\,dt}$$

where ΔHbO_2 is the change in haemoglobin concentration measured by NIRS in time t, $\Delta f Sp_{O_2}$ is the change in fractional arterial oxygen saturation and K is a constant incorporating blood haemoglobin concentration, molecular mass of haemoglobin and cerebral tissue density. This converts the units for CBF from µmol $litre^{-1}$ s^{-1} to ml 100 g^{-1} min^{-1}. As part of the CBF calculation procedure approximately 30 % of measurements are typically rejected on the basis of an excessively varying baseline Hbsum, end-tidal carbon dioxide or MAP. These aspects and others comprising the theoretical basis of the technique in adults have been discussed previously in detail [15].

STATISTICAL ANALYSIS

The values for CBF in conscious and anaesthetized subjects were compared using an unpaired *t* test. The values for CBF measured on the scalp and on the dura were compared with a paired *t* test.

Results

With the optical fibres positioned on the scalp, the mean CBF in the conscious subjects was 17 (SD 7) ml 100 g^{-1} min^{-1} compared with 21 (8) ml 100 g^{-1} min^{-1} in the anaesthetized subjects ($P > 0.1$). In the seven patients in whom CBF was measured on the dura, mean CBF with the fibres on the dura was 68 (21) ml 100 g^{-1} min^{-1} $P < 0.0001$ compared with the scalp. The values for CBF, heart rate and end-tidal carbon dioxide in the conscious volunteers are given in table 1. The values for mean end-tidal carbon dioxide and MAP in each anaesthetized subject are shown in table 2 together with the mean value for CBF in each subject. Table 3 shows the paired values for CBF measured on the scalp and dura during anaesthesia with the corresponding values for end-tidal carbon dioxide and MAP. Data collected during a typical

Table 1 Age and mean values for cerebral blood flow (CBF), heart rate and end-tidal (ET) or transcutaneous pco_2 ($TCco_2$) in conscious subjects. n = number of CBF measurements

Subject	Age	CBF (ml 100 g^{-1} min^{-1}) Mean (SD)	n	Heart rate (beat min^{-1}) Mean (SD)	ET/$TCco_2$(*) (kPa) Mean (SD)
1	21	23 (12)	7	67 (1)	4.2 (0.3)
2	29	9 (4)	6	63 (1)	4.7 (0.3)
3	44	17 (9)	5	60 (3)	4.5 (0.3)
4	29	16 (7)	5	55 (1)	3.0 (0)
5	27	10 (4)	5	61 (5)	4.1 (0.4)
6	28	12 (3)	3	65 (10)	4.5 (0.5)
7	26	10 (3)	6	67 (2)	4.3 (0.1)*
8	36	15 (10)	4	68 (3)	5.5 (0.1)*
9	36	23 (11)	4	69 (3)	4.3 (0.1)*
10	22	19 (9)	4	56 (4)	7.2 (0.3)*
11	29	30 (10)	6	84 (2)	5.7 (0.1)*
Mean (SD)	30 (6)	17 (7)	5	65 (8)	4.7 (1.1)

Table 2 Age, diagnosis and mean values for cerebral blood flow (CBF), mean arterial pressure (MAP) and end-tidal CO_2 ($ETco_2$) in anaesthetized subjects. (HS = Hippocampal sclerosis; DNET = dysembroplastic neuroepithelial tumour)

Subject	Diagnosis	Age	CBF (ml 100 g^{-1} min^{-1}) Mean (SD)	n	MAP (mm Hg) Mean (SD)	$ETco_2$ (kPa) Mean (SD)
1	HS	48	23 (7)	3	82 (4)	4.5 (0.1)
2	HS	19	30 (3)	4	68 (4)	4.0 (0.1)
3	HS	25	26 (2)	3	63 (1)	4.0 (0.1)
4	DNET	39	30 (18)	3	59 (1)	5.3 (0.1)
5	HS	37	16 (3)	3	79 (5)	5.3 (0.1)
6	HS	34	13 (8)	4	72 (2)	4.5 (0.1)
7	HS	34	9 (3)	5	78 (5)	5.3 (0.1)
8	HS	31	22 (10)	4	57 (3)	5 (–)
9	HS	29	28 (9)	4	74 (9)	3.8 (0.3)
10	HS	21	21 (13)	4	81 (1)	6.7 (1.8)
Mean		32 (9)	21 (8)	4	71 (9)	4.7 (0.8)

Table 3 Mean values for cerebral blood flow (CBF), end-tidal ($ETco_2$) and arterial pressure (MAP) in anaesthetized subjects measured both on the scalp and on the dura

	Scalp				Dura			
Subject	CBF (ml 100 g^{-1} min^{-1}) Mean (SD)	n	ET/$TCco_2$ (kPa) Mean (SD)	MAP (mm Hg) Mean (SD)	CBF (ml 100 g^{-1} min^{-1}) Mean (SD)	n	ET/$TCco_2$ (kPa) Mean (SD)	MAP (mm Hg) Mean (SD)
1	23 (7)	3	4.5 (0.1)	82 (4)	65 (6)	5	4.1 (0.1)	71 (1)
2	30 (3)	4	4.0 (0.1)	68 (4)	67 (13)	4	4.1 (0.4)	93 (2)
3	26 (2)	3	4.0 (0.1)	63 (1)	95 (34)	5	5.4 (0.3)	64 (2)
4	30 (18)	3	5.3 (0.1)	59 (1)	79 (49)	5	5.4 (0.3)	57 (2)
5	16 (3)	3	5.3 (0.1)	79 (5)	27 (4)	4	4.5 (0.3)	72 (3)
6	13 (8)	3	4.5 (0.1)	72 (2)	73 (35)	4	4.1 (0.1)	72 (2)
7	9 (3)	5	5.1 (0.1)	78 (5)	70 (18)	4	4.9 (0.1)	77 (3)
Mean	21 (8)	3	4.6 (0.5)	72 (9)	68 (21)	4	4.6 (0.7)	72 (11)

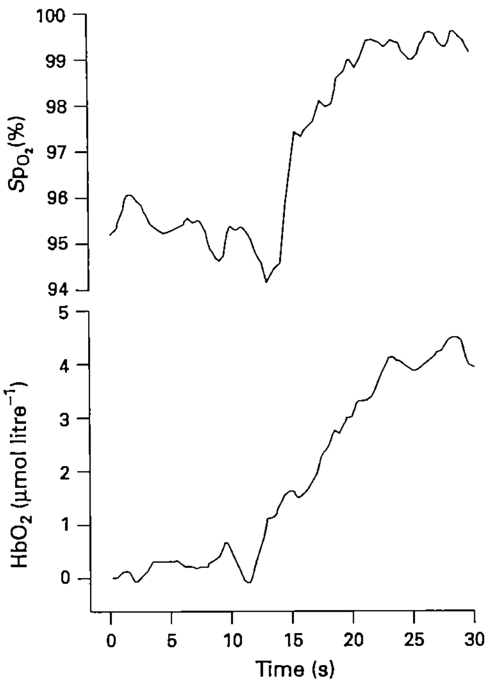


Figure 1 Representative data collected from an anaesthetized subject during a CBF measurement. The temporal offset between the increase in HbO_2 concentration and the increase in Sp_{O_2} is a result of the faster arrival of the tracer in the cerebral circulation than at the earlobe.

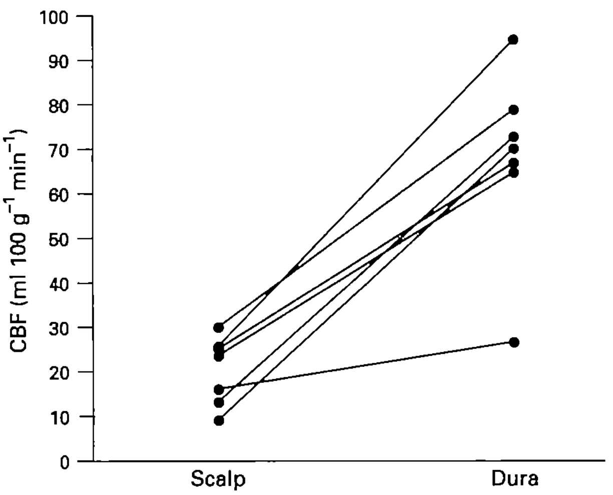


Figure 2 Cerebral blood flow (CBF) measured on the scalp and dura by NIRS in seven subjects.

CBF measurement are shown in figure 1 and the paired data for CBF on the scalp and dura are shown in figure 2.

Discussion

We have obtained non-invasive estimates of CBF using NIRS in adult subjects with the optodes placed on the scalp and directly on the dura. There are several assumptions underlying the use of NIRS to estimate CBF. In particular we have assumed that over the short period of the measurement (4 s) the small quantity of additional oxyhaemoglobin which enters the cerebral circulation acts as an inert tracer, and causes no significant effect on $CMRO_2$, CBF or cerebral blood volume (CBV). Previous physiological studies have shown that CBF is virtually constant when arterial oxygen tension varies between 5.7 and 12.3 kPa [16]. Furthermore, during our measurements the total cerebral haemoglobin concentration ([Hbsum]) was seen to remain constant, suggesting that, despite rapid changes in Sp_{O_2}, there had been no significant change in CBV. Finally, it is well known that, provided Sp_{O_2} is maintained within the physiological range, and brain metabolic requirements are being met, an increase in cerebral oxygen delivery does not result in an increase in oxygen extraction [17]. In these circumstances the small additional increment in HbO_2 concentration can be justifiably regarded as an inert tracer. This is discussed further elsewhere [9].

The values obtained for CBF when the optical fibres were positioned on the scalp were much lower than those obtained by invasive techniques, such as the i.v. ^{133}Xe washout technique [18], the Kety-Schmidt method [19], or by positron emission tomography (PET) [20]. However, the measured values for CBF when the optodes were positioned directly on the dura are in close agreement with those obtained using other established methods. Kety and Schmidt estimated mean CBF as 54 (12) ml 100 g^{-1} min^{-1} [21]. In healthy young men, a typical value by ^{133}Xe washout is 48 (7) ml 100 g^{-1} min^{-1} [18] and a typical value for grey matter by PET is 55 ml 100 g^{-1} min^{-1} [20].

The underestimation of CBF when the fibres were placed on the scalp is probably caused by the effects of extracerebral tissue on the transmission of light through the cranial cavity. Although it is a fundamental principle of NIRS that biological tissue is translucent to infrared light, nevertheless photons crossing the head travel on a path substantially longer than the linear distance between their points of entry and exit because of the scattering effect mentioned above. The true pathlength has been measured as 5.9 times greater than the linear pathlength (the interoptode spacing) in the adult head.

When this pathlength factor (DPF) is known, the distance that light has travelled through the head can be inserted into the Lambert-Beer equation and changes in haemoglobin concentration can be quantified. Computer modelling of near infrared light propagation in the adult head suggests that extracerebral tissue contributes 60–70 % of the total optical pathlength [22] but has very little blood flow (around 5–8 ml 100 g^{-1} min^{-1} [23]). When a rapid change in Sp_{O_2} is induced in order to make a measurement of CBF, the change in haemoglobin concentration occurs almost entirely in the cerebral tissue over the 4-s period of the measurement, since the blood flow to extracerebral tissue is so low. As cerebral tissue occupies only 30–40 % of the illuminated tissue volume the true CBF is thus underestimated by a factor which is equal to the ratio of the optical pathlength in brain compared with the total optical pathlength. When the optical fibres are placed directly on the dura the extracerebral component of the pathlength is reduced to zero and there is therefore no underestimation of CBF. Our results suggest that there is an approximately threefold underestimate of CBF with fibres on the scalp.

As the effects of extracerebral tissues are likely to be relatively consistent between different subjects, reliable comparisons of measurements between and within patients may be possible. In future it may be possible to determine directly the contribution of extracerebral tissue to the total optical pathlength in each subject, thus enabling CBF measurements obtained by NIRS from the scalp to be compared directly with measurements obtained by other techniques.

We did not observe a significant change in CBF as a result of anaesthesia in our study whereas there was a significant (approximately threefold) increase in CBF values measured on the dura in all except one patient. Mean arterial pressure was assumed to be in the normal range in the conscious objects and was not measured; the values for heart rate are normal supporting this assumption. The difference between end-tidal carbon dioxide, and Pa_{CO_2} is unlikely to have introduced a significant error. The mean end-tidal carbon dioxide of the anaesthetized group was the same as that of the conscious subjects (4.7 kPa). There was no significant difference in mean end-tidal carbon dioxide between measurements on the scalp and on the dura but it is notable that the patient with the smallest difference between scalp and dura CBF (patient 5) exhibited a decrease in end-tidal carbon dioxide and the patient with the greatest change (patient 3) exhibited an increase in end-tidal carbon dioxide. Two patients had arterial pressures which were close to the lower end of the autoregulatory range but in both cases the values for MAP on the scalp and dura were almost identical. The neuropathological diagnoses in the anaesthetized group were unlikely to have influenced CBF.

The drugs used during anaesthesia are thought to have minimal effects on CBF. In human studies to date, fentanyl [24] has not been observed to cause a significant increase in CBF, although in one study, when given at a dose of 10 μg kg^{-1} it caused a decrease [25]. Similarly, the administration of isoflurane is not associated with an increase in CBF when administered in nitrous oxide to a combined MAC of 1.5 [26, 27]. No patient in our study received an inspired isoflurane concentration greater than 1.1% in 60% nitrous oxide (i.e. a combined MAC of 1.7) and most received less. In each patient the end-tidal isoflurane concentration was maintained at a constant value for both sets of measurements.

The evidence on the effect of nitrous oxide on CBF is less clear although there is a tendency for CBF to increase during anaesthesia. In one recent study, CBF was measured by ^{133}Xe washout in volunteers during the inhalation of 30% and 50% nitrous oxide. CBF was said to be significantly greater breathing nitrous oxide than air although absolute values were not given [28]. In another study also using ^{133}Xe washout, patients receiving 35% oxygen in air or nitrous oxide, supplemented with isoflurane, nitrous oxide caused an increase in CBF from 40 to 57 ml 100 g^{-1} min^{-1} [29], a 43% rise. Our study showed an increase of 24% from 17 to 21 ml 100 g^{-1} min^{-1} but this was not statistically significant. In summary, we are not able to demonstrate a significant effect of general anaesthesia on CBF with the present technique.

We conclude that NIRS has the potential to provide non-invasive bedside assessment of CBF in adult subjects when the contribution of surface tissues to the differential pathlength factor in each individual studied is quantified. Although the values obtained from the scalp appear to underestimate the true CBF because of the optical effect of the extracerebral tissues, the technique allows comparison of measurements between and within subjects. In neurosurgical procedures involving craniotomy NIRS allows intraoperative measurement of CBF with the optical fibres positioned on the dura. The values thus obtained are in close agreement with those obtained by other means. Although further validation studies are required this technique appears to have potential for the non-invasive, bedside assessment of cerebral perfusion.

Acknowledgements

This work was carried out at University College London Hospitals and The National Hospital for Neurology and Neurosurgery, London, UK. The work was supported by the Medical Research Council, The Wolfson Trust and Hamamatsu Photonics (UK) Ltd. Parts of the data have been presented in abstract form at the Anaesthetic Research Society (Liverpool, UK, 1994) and the Society of British Neurological Surgeons (Dundee, UK, 1994).

We thank Dr Fenella Kirkham and Dr Penny Fallon of the Hospital for Sick Children, Great Ormond Street for the loan of the NIRS equipment for part of the study. This work was supported by the Wolfson Foundation, the Medical Research Council and Hamamatsu Photonics (UK).

References

1. Jöbsis FF. Noninvasive monitoring of cerebral oxygenation and myocardial oxygen sufficiency and circulatory parameters. *Science* 1977; **198**: 1264–1267.
2. Wyatt JS, Cope M, Delpy DT, Wray S, Reynolds EOR. Quantification of cerebral oxygenation and haemodynamics in sick newborn infants by near infrared spectrophotometry. *Lancet* 1986; **2**; 1063–1066.
3. Wyatt JS, Cope M, Delpy DT, Richardson CE, Edwards AD, Wray S, Reynolds EOR. Quantification of cerebral blood volume by near infrared spectroscopy. *Journal of Applied Physiology* 1990; **68** (3): 1086–1091.
4. Edwards AD, Wyatt JS, Richardson CE, Delpy DT, Cope M, Reynolds EOR. Cotside measurement of cerebral blood flow in ill newborn infants by near infrared spectroscopy. *Lancet* 1988; **2**: 770–771.
5. Wyatt JS, Edwards AD, Cope M, Delpy DT, McCormick DC, Reynolds EOR. Response of cerebral blood volume to changes in arterial carbon dioxide tension in preterm and term infants. *Pediatric Research* 1991; **29**: 553–557.
6. Roberts I, Fallon P, Kirkham FJ, Lloyd-Thomas A, Cooper C, Maynard R, Elliot M, Edwards ADE. Estimation of cerebral blood flow with near infrared spectroscopy and indocyanine green. *Lancet* 1994; **342**: 1425.
7. Skov L, Pryds O, Greisen G. Estimating cerebral blood flow in newborn infants: Comparison of near infrared spectroscopy and ^{133}Xe clearance. *Pediatric Research* 1991; **30**: 570–573.
8. Bucher H-U, Edwards AD, Lipp AE, Duc G. Comparison between near infrared spectroscopy and ^{133}Xe clearance for estimation of cerebral blood flow in critically ill preterm infants. *Pediatric Research* 1993; **33**: 56–60.

9. Elwell CE, Cope M, Edwards AD, Wyatt JS, Delpy DT, Reynolds EOR. Quantification of cerebral haemodynamics by near infrared spectroscopy. *Journal of Applied Physiology* 1994; **77**: 2753–2760.
10. Edwards AD, Richardson C, van der Zee P, Elwell CE, Wyatt JS, Cope M, Delpy DT, Reynolds EOR. Measurment of haemoglobin flow and blood flow by near infrared spectroscopy. *Journal of Applied Physiology* 1993; **75**: 1884–1889.
11. Wray S, Cope M, Delpy DT, Wyatt JS, Reynolds EOR. Characterisation of the near infrared absorption spectrum of cytochrome aa$_3$ and haemoglobin for the noninvasive monitoring of cerebral oxygenation. *Biochimica et Biophysica Acta* 1988; **933**: 184–192.
12. Essenpreiss M, Elwell CE, van der Zee P, Cope M, Delpy DT. Spectral dependence of temporal point spread function in human tissues. *Applied Optics* 1993; 32 (4): 418–425.
13. van der Zee P, Cope M, Arridge SR, Essenpreiss M, Potter LA, Edwards AD, Wyatt JS, McCormick DC, Roth SC, Reynolds EOR, Delpy DT. Experimentally measured optical pathlengths for the adult head, calf and forearm and the head of the newborn infant as a function of interoptode spacing. *Advances in Experimental Medicine and Biology* 1992; **416**: 143–153.
14. Cope M, Delpy DT, Reynolds EOR, Wray S, Wyatt J, van der Zee P. Methods of quantitating cerebral near infrared spectroscopy data. *Advances in Experimental Medicine and Biology* 1988; **222**: 183–189.
15. Leenders KL, Perani D, Lammertsma AA, Heather JD, Buckingham P, Healy MJR, Gibbs JM, Wise RJS, Hatazawa J, Herold S, Beaney RP, Brooks DJ, Spinks T, Rhodes C, Frackowiak RSJ, Jones T. Cerebral blood flow, blood volume and oxygen utilisation. Normal values and effect of age. *Brain* 1990; **113**: 27–47.
16. Siesjö BK. *Brain Energy Metabolism*. Chichester: Wiley, 1978.
17. Connett RJ, Honig CR, Gayeski TEJ, Brooks GA. Defining hypoxia: a systems review of VO$_2$, glycolysis, energetics and intracellular PO$_2$. *Journal of Applied Physiology* 1990; **68** (3): 833–842.
18. Obrist WD, Wilson WE. Regional cerebral blood flow measurements in humans by ^{133}Xe clearance. *Cerebrovascular and Brain Metabolism Reviews* 1990; **2**: 283–327.
19. Kety SS, Schmidt CF. Determination of cerebral blood flow in man by the use of nitrous oxide in very low concentrations. *American Journal of Physiology* 1945; **143**: 53–66.
20. Frackowiak RSJ, Jones T, Heather JD. Quantitative measurement of regional cerebral blood flow and oxygenation metabolism in man using ^{15}O and positron emission tomography: theory, procedure and normal values. *Journal of Computer Assisted Tomography* 1980; **4**: 727–736.
21. Kety SS, Schmidt CF. The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedure and normal values. *Journal of Clinical Investigations* 1948; **27**: 476–483.
22. Hiraoka M, Firbank M, Essenpreiss M, Cope M, Arridge SR, van der Zee P, Delpy DT. A Monte Carlo investigation of optical pathlength in inhomogeneous tissue and its application to near infrared spectroscopy. *Physics, Medicine and Biology* 1993; **38**: 1859–1876.
23. Friberg L, Kastrup J, Hansen M, Bülow J. Cerebral effects of scalp cooling and extracerebral contribution to calculated blood flow values using the intravenous ^{133}Xenon technique. *Scandinavian Journal of Clinical Investigation* 1986; **46**: 375–379.
24. Vernhiet J, Macrez P, Renou AM, Constant P, Billerey J, Caille JM. Effects of high doses of morphinomimetics on the cerebral circulation in normal subjects. *Annales Anesthesiologique Française* 1977; **18**: 803–810.
25. Vernhiet J, Renou AM, Orgogozo JM, Constant P, Caille JM. Effects of diazepam–fentanyl mixture on cerebral blood flow and oxygen consumption in man. *British Journal of Anaesthesia* 1978; **50**: 165–169.
26. Eintrei C, Lezniewski W, Carlsson C. Local application of ^{133}Xenon for measurement of regional cerebral blood flow (rCBF) during halothane, enflurane and isoflurane anaesthesia in humans. *Anaesthesiology* 1985; **63**: 391–394.
27. Madsen JB, Cold GE, Hansen ES, Bardrum B. The effect of isoflurane on cerebral blood flow and metabolism in humans during craniotomy for small supratentorial tumours. *Anaesthesiology* 1987; **66**: 332–336.
28. Field LM, Dorrance DE, Krzeminska EK, Barsoum LZ. Effect of nitrous oxide on cerebral blood flow in normal humans. *British Journal of Anaesthesia* 1990; **70**: 154–159.
29. Algotsson L, Messeter K, Rosen I, Holmin T. Effects of nitrous oxide on cerebral haemodynamics and metabolism during isoflurane anaesthesia in man. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 46–52.

British Journal of Anaesthesia 1996; 76: 49–53

Effect of transdermal hyoscine on nausea and vomiting during and after middle ear surgery under local anaesthesia

P. HONKAVAARA

Summary

The efficacy of transdermal hyoscine in the reduction of nausea, retching and vomiting was compared with placebo during and after stapedo- and tympanoplasty under local anaesthesia in a double-blind, prospective and randomized study. In the placebo group ($n = 29$), 69% of the patients were free from emetic symptoms during and 41% after the operation. The corresponding figures were 93% ($P < 0.05$) and 74% ($P < 0.05$) in the hyoscine group ($n = 27$). The patients in the placebo group needed more droperidol during and after operation ($P < 0.05$). The frequency of side effects was similar in both groups. In posturography the patients with emetic sequelae in the placebo group had a markedly deteriorated upkeep of posture ($P < 0.05$) measured as body sway velocities. A strong correlation was found between motion sickness and emetic sequelae after surgery, and patients with a history of motion sickness benefited most from hyoscine. (*Br. J. Anaesth.* 1996; **76**: 49–53).

Key words

Vomiting, nausea. Vomiting, antiemetics. Surgery, otolaryngological. Premedication, hyoscine. Drug delivery, transdermal.

Introduction

Hyoscine was found to reduce postoperative nausea and vomiting (PONV) in two recent studies after middle ear surgery under general anaesthesia [1, 2]. The percentages of patients suffering from PONV in the placebo groups were 80% and 62%. Although vertigo and dizziness are well known complications after stapedoplasty [3] no study has been published on emetic symptoms and middle surgery under local anaesthesia.

Assessment of earlier studies performed in our clinic indicated that stapedoplasty caused considerable PONV while tympanoplasty produced a little less. Transdermal hyoscine has been shown to be antiemetic both in motion sickness [4] and postoperatively after different types of surgery [1, 2, 5–9]. One of the many causes of PONV [10] may be increased stimulation of the vestibular apparatus by surgery, and this could be enhanced further by increased vestibular sensitivity caused by opioids [11, 12]. Any possible vestibular component to PONV and its modification by transdermal hyoscine might be revealed by computerized posturography [13, 14].

Thus, the present work was designed to study the occurrence of PONV and need for rescue antiemetics during and after stapedo- and tympanoplasties performed under local anaesthesia and the effect of transdermal hyoscine.

Patients and methods

Informed consent was obtained from 56 ASA class I–II patients, aged 21–55 yr, scheduled for stapedo- or tympanoplasty under local anaesthesia. Exclusion criteria included: regular or temporary use of antiemetic drugs, and vomiting or retching within 24 h before the operation. The Ethics Committee of the Otolaryngological Hospital approved the study.

Patients were allocated randomly to a placebo ($n = 29$) or a hyoscine ($n = 27$) group in a double-blind study. On the afternoon of the day before surgery, a history of motion sickness and PONV and the menstrual data [10, 15] were noted. Thereafter, on the basis of the randomization, either an inactive patch or an identical hyoscine patch (Scopoderm 0.5 mg 72 h^{-1}) was applied to the skin of the postauricular area opposite the operative side after cleansing the skin with diethyl ether. In order to secure the patch, it was covered by an adhesive tape.

Evaluation of postural stability by computerized posturography [16] was performed as follows: (1) before applying the test patch during the afternoon before operation, (2) before premedication on the morning of the operation, (3) 24 h after surgery and (4) 1 week after the operation. In posturography, the patient stands on a force platform connected to a computer. The system records the movement of the centre-point of forces (the sway path). The calculated length of the sway path during analysis gives the mean sway velocity [17]. The posturographies were made under a 3-min sequence, during which the recordings were made with both the eyes open and closed for 30 s after a period of initial stabilization for both eyes open and closed. Patients with uncompensated vestibular function before surgery (mean sway velocity over 3 cm s^{-1} during the control recording (1) with their eyes closed), were excluded from statistical processing of the results of posturography: two from the placebo group and four from the hyoscine group. The Romberg quotient is

---

P. HONKAVAARA, MD, Department of Anaesthesia, Otolaryngological Hospital, University of Helsinki, Haartmaninkatu 4E, SF-00290 Helsinki, Finland. Accepted for publication: August 1, 1995.

a derived ratio between mean sway velocity values recorded in non-visual and visual conditions and it is used commonly to describe the effect of visual control on posture. The repeatability of the posturography as a test of postural stability has been shown to be good [18].

Before local anaesthesia the patients were questioned on the presence of sedation, dry mouth, anxiety, dizziness, blurred vision, urinary difficulties or other symptoms. Thereafter, the placebo group received glycopyrronium 0.2 mg i.v. and the hyoscine group received saline from identical syringes containing the same volume, each with its own code number in a double-blind manner.

Premedication comprised oxycodone 0.1 mg kg^{-1} i.m. 40–60 min before operation. Local anaesthesia was performed with lignocaine containing adrenaline. Fentanyl 1 µg kg^{-1} was given before local anaesthesia and thereafter during operation as 25-µg doses for analgesia. Diazepam in 2.5-mg doses was used for sedation, if needed. Monitoring before, during and after operation included arterial pressure with automatic oscillotonometer, electrocardiogram and haemoglobin oxygen saturation (Sp_{O_2}). During operation patients received oxygen 2–4 litre min^{-1} via nasal cannulae.

Postoperative pain was treated with diclofenac 1 mg kg^{-1} i.v. or with paracetamol 10 mg kg^{-1} suppositories in patients who could not tolerate diclofenac. In addition, oxycodone 0.05 mg kg^{-1} i.v. or 0.1 mg kg^{-1} i.m. was used if needed. (Note that diclofenac is registered in Finland for i.v. use, but this is not the case in all countries.)

A trained nurse, who was unaware of the nature of the study drug, enquired for vertigo and assessed the occurrence of nausea, retching and vomiting during operation and at the following times; 0–2, 2–6, 6–12, 12–18 and 18–24 h after the end of the surgery. If the patient experienced more than one symptom, for example both nausea and vomiting, she was listed as having vomited. During the first 0–2 h after surgery the patients were in the recovery room and thereafter in the ward. Droperidol 10 µg kg^{-1} i.v. or i.m. was given for vomiting, retching or prolonged nausea, at a minimum interval of 30 min. Vertigo was scored as follows: 0 = no vertigo, 1 = slight sensation of vertigo, 2 = strong sensation of vertigo, 3 = has to avoid head movement and 4 = has to keep eyes closed.

STATISTICS

ANOVA, followed by the Bonferroni/Dunn procedure, if appropriate, was used for parametric data, and the chi-square test with Yates' correction or Fisher's exact test for non-parametric data. Logistic regression analysis was used to find predictors for PONV. The Spearman rank correlation coefficient was applied to the posturography data. A P value less than 0.05 was regarded as significant.

Results

There were no significant differences in patient characteristics or details of the local anaesthesia between the groups (table 1). The number of female patients having normal menstrual cycles was 15 in the placebo group and 14 in the hyoscine group. The distribution of the patients between the different phases of the menstrual cycle was similar in both groups.

Table 1 Characteristics of patients undergoing stapedo- and tympanoplasty, mean values (SD or range). No statistical differences between groups

	Placebo	Hyoscine
Patients (n)	29	27
Stapedo-/tympanoplasty	23/6	20/7
Sex (M/F)	11/18	12/15
Age (yr)	41 (21–55)	38 (22–53)
Weight (kg)	70 (18)	71 (12)
Duration of operation (min)	73 (20)	78 (21)
Peroperative drugs		
Fentanyl (µg kg^{-1})	1 (0.3)	1 (0.2)
Diazepam (mg kg^{-1})	0.046 (0.041)	0.033 (0.038)
Lignocaine (mg kg^{-1})	1, 24 (0.38)	1, 18 (0.29)
Postoperative oxycodone		
No. of patients	10	13
Median dose (mg kg^{-1})	0.11 (0.10–0.29)	0.10 (0.04–0.50)

Table 2 Percentage of patients suffering from emetic symptoms during and after stapedo- and tympanoplasty under local anaesthesia receiving preoperatively either a placebo or hyoscine patch, *$P < 0.05$ compared with placebo group

	Placebo	Hyoscine
Patients (n)	29	27
Peroperatively		
No symptoms	69	93*
Nausea	21	7
Retching	0	0
Vomiting	10	0
Mean number of nausea and vomiting (SD)	0.41 (0.73)	0.07 (0.27)*
Postoperatively		
No symptoms	41	74*
Nausea	17	7
Retching	14	0
Vomiting	28	19

In logistic regression analysis the following variables were found to be predictors for PONV: sex ($P < 0.001$), vertigo score ($P < 0.001$), history of motion sickness ($P < 0.05$), treatment with hyoscine patch ($P < 0.05$) and the other variables studied were not predictors for PONV.

During operation 69 % of patients in the placebo group were devoid of nausea and vomiting and the corresponding value for the hyoscine group was 93 % ($P < 0.05$). No retching occurred during operation. Patients in the placebo group had more emetic episodes peroperatively than the patients in the hyoscine group ($P < 0.05$) (table 2).

During the first 24 h after surgery the number of patients having any emetic symptoms was less (7/27 *vs* 17/29, $P < 0.05$) in the hyoscine group than in the placebo group (table 2).

Both the number of patients needing and the number of doses needed of the rescue antiemetic (droperidol) was significantly higher in the placebo group during operation, in the ward (2–24 h) and for the whole study. There was no significant difference in the time from local anaesthesia to the need for droperidol (table 3).

Table 3 Need for rescue antiemetic (10 μg kg^{-1} droperidol) during and after operation of stapedo- and tympanoplasty under local anaesthesia (mean (SD)), * $P < 0.05$ between placebo and hyoscine groups. ** $P = 0.096$.

	Placebo	Hyoscine
Patients (*n*)	29	27
Patients needing droperidol (%)		
peroperatively	31	7*
0–2 h	21	11
2–24 h	41	11*
total	59	22*
Number of doses of droperidol mean (SD)		
peroperatively	0.31 (0.54)	0.07 (0.27)*
0–2 h	0.28 (0.65)	0.11 (0.32)
2–24 h	0.48 (0.69)	0.19 (0.62)**
total	1.01 (1.49)	0.36 (1.00)*
Time from local anaesthesia to need for droperidol (min)	335 (335)	215 (175)

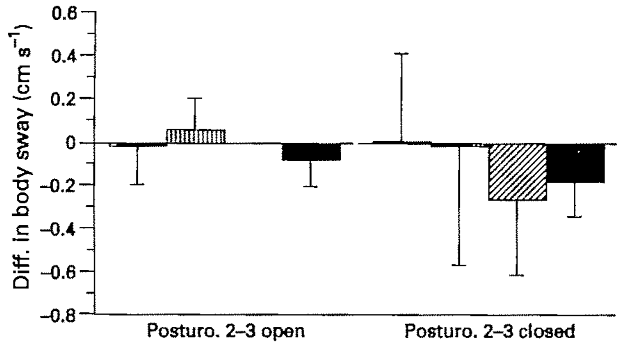


Figure 1 Differences in mean body sway in posturographies (Posturo.) 2 and 3 eyes open and closed, in the placebo and hyoscine groups when grouped in relation to retching and vomiting after surgery (mean, SD). □ = Placebo group with no retching and vomiting, ▥ = placebo group with retching and vomiting, ▨ = hyoscine group with no retching and vomiting, ■ = hyoscine group with retching and vomiting.

Posturographies 2 (in the morning before surgery) and 3 (24 h after surgery) revealed in the placebo group significantly more deterioration of postural stability in the patients suffering from retching and vomiting than in the patients without these symptoms. Both the differences in mean sway velocities ($P < 0.05$) and Romberg quotient ($P < 0.05$) had worsened, when rankings from differences in these recordings were assessed by Spearman rank correlation coefficient. In the hyoscine group there were no significant changes when postural stability was assessed in a similar fashion. There were no significant differences in the hyoscine group between the patients with or without emetic sequelae before and after administration of the hyoscine patch (posturographies 1 and 2). Figure 1 illustrates the mean differences in body sway velocities in different groups (posturographies 2 and 3), but it should be noted that statistically the *rankings* of the differences are assessed.

There were 12 patients in the placebo group and nine patients in the hyoscine group with a positive history of motion sickness and the respective values for negative history of PONV were 16 and 13. The cross-tabulated results of the correlations between treatment, history of motion sickness and history of PONV are shown in table 4. Hyoscine significantly increased the percentage of patients who were free of all emetic symptoms both during and after surgery ($P < 0.05$). The respective increase was also significant in relation to negative history of PONV and being symptom-free during surgery ($P < 0.05$). In the placebo group there was a positive correlation between a history of motion sickness and nausea and vomiting during ($P < 0.001$) and after surgery ($P < 0.005$). There was no significant effect of a history of motion sickness on nausea and vomiting in the hyoscine group, when assessed in a similar fashion. In all groups there was no correlation between positive histories of PONV and motion sickness.

Table 4 Percentage of patients free from all emetic symptoms in relation to histories of PONV (hPONV) and motion sickness (hMoSi), * $P < 0.05$ between placebo and hyoscine groups ** $P = 0.0524$.

	Placebo	Hyoscine
	During surgery free from all emetic symptoms (%)	
hMoSi negative	94	94
hMoSi positive	33	89*
hPONV negative	69	100*
hPONV positive	83	82
	After surgery free from all emetic symptoms (%)	
hMoSi negative	65	78
hMoSi positive	8	67*
hPONV negative	44	85**
hPONV positive	33	55

In the placebo group 14% of the patients reported sedation before local anaesthesia and the corresponding value was 4% in the hyoscine group. During the 24 h after surgery more patients in the placebo group reported vertigo (8/29) than in the hyoscine group (1/27, $P < 0.05$). There were no significant differences in side effects immediately before local anaesthesia between placebo and hyoscine groups and they varied between 0–11%.

Discussion

Transdermal hyoscine considerably increased the percentage of patients who were free from all emetic symptoms, and decreased the need for rescue antiemetic during and after stapedo- and tympanoplasties under local anaesthesia without increasing the frequency of side effects compared with the placebo group. The most clinically important finding was a reduced incidence of nausea and vomiting during operation, because emetic symptoms normally result in movement, which may lead to serious consequences during surgical manipulation in the middle ear.

The use of glycopyrronium in the placebo group, in order to diminish salivation and thus to reduce the possibility of head movements during ear microsurgery caused by swallowing, may raise doubts about the design of the study. However, glycopyrronium is unable to cross the blood-brain barrier [19] and those muscarinic receptor antagonists that are effective in reducing nausea and vomiting act by blocking central muscarinic receptors in afferent pathways of the vomiting reflex [20]. Glycopyrronium has been shown not to affect gastric emptying and intestinal transit times [21]. The overall percentage of placebo-treated patients reporting emetic symptoms in this study was also the same as that in two recently published studies on PONV after middle ear surgery under general anaesthesia [1, 2]. Drugs effective in motion sickness include centrally acting muscarinic receptor antagonists [22] and there are no data suggesting that glycopyrronium affects the vestibular system [23]. Furthermore, it was given approximately 4 min before local anaesthesia with lignocaine containing adrenaline and the increase in pulse rate was masked by the tachycardia caused by the local anaesthesia.

The results of this study are in agreement with earlier studies showing that transdermal hyoscine is an effective prophylactic against PONV [1, 2, 5–9]. In the present study, the patients in the placebo group with a history of motion sickness had a higher frequency of nausea and vomiting than the patients without motion sickness and this finding has also been reported elsewhere [1, 24, 25]. The reduction in nausea and vomiting in the hyoscine group, in relation to motion sickness may result from specific inhibition of the post-synaptic potential in the neurones of the vestibular nuclei [14]. This assumption is supported by the fact that in the placebo group there was a significant correlation between motion sickness and nausea and vomiting during and after surgery but this was not the case in the hyoscine group.

Posturography revealed that the patients in the placebo group not suffering from retching and vomiting, had better vestibulo-spinal function after surgery than those suffering from these symptoms. In the hyoscine group there was no difference in deterioration in postural stability between those without emetic and those with emetic sequelae (retching and vomiting), which also supports a direct action of hyoscine on the vestibular system [14].

In a recently published study on the effect of transdermal hyoscine on PONV after outpatient ear surgery there was, in common with this study, both more PONV and vertigo in the placebo group [2]. In a recently published study on postoperative nystagmus and nausea [26] there was a marked correlation between PONV and nystagmus, which is also caused by vestibular dysfunction. The recordings were made earlier than in our study: the first after the patient was oriented to time and space in the recovery room and the second soon after arrival in the short-procedure unit. As described earlier [1], because the frequency of PONV after ear surgery declines throughout the first 24 h after operation it is possible that posturography performed 24 h after surgery was too late to reveal the real magnitude of correlation between PONV and postural instability. Vestibular symptoms in the form of imbalance and occasional dizziness have been reported to last weeks after surgery [3].

Acknowledgement

I acknowledge the numerous discussions with the Professor in Otology, Ilmari Pyykkö, MD, during the preparation of the programme of posturography for this study, during assessment of the results of posturographies and during the revision of the manuscript.

References

1. Honkavaara P, Saarnivaara L, Klemola U-M. Prevention of nausea and vomiting with transdermal hyoscine in adults after middle ear surgery during general anaesthesia. *British Journal of Anaesthesia* 1994; **73**: 763–766.
2. Reinhart DJ, Klein KW, Schroff E. Transdermal scopolamine for the reduction of postoperative nausea in outpatient ear surgery: a double-blind, randomized study. *Anesthesia and Analgesia* 1994; **79**: 281–284.
3. Silverstein H, Rosenberg S, Jones R. Small fenestra stapedotomies with and without KTP laser: A comparison. *Laryngoscope* 1989; **99**: 485–488.
4. Cronin CM, Sallan SE, Wolfe L. Transdermal scopolamine in motion sickness. *Pharmacotherapy* 1982; **2**: 29–31.
5. Honkavaara P, Saarnivaara L, Klemola U-M. Effect of transdermal hyoscine on nausea and vomiting after surgical correction of prominent ears under general anaesthesia. *British Journal of Anaesthesia* 1995; **74**: 647–650.
6. Kotelko DM, Rottman RL, Wright WC, Stone JJ, Yamashiro AY, Rosenblatt RM. Transdermal scopolamine decreases nausea and vomiting following cesarean section in patients receiving epidural morphine. *Anesthesiology* 1989; **71**: 675–678.
7. Semple P, Madej TH, Wheatley RG, Jackson IJB, Stevens, J. Transdermal hyoscine with patient-controlled analgesia. *Anaesthesia* 1992; **47**: 399–401.
8. Bailey PL, Streisand JB, Pace NL, Bubbers SJM, East KA, Mulder S, Stanley TH. Transdermal scopolamine reduces nausea and vomiting after outpatient laparoscopy. *Anesthesiology* 1990; **72**: 977–980.
9. Horimoto Y, Tomie H, Hanzawa K, Nishida Y. Scopolamine patch reduces postoperative emesis in paediatric patients following strabismus surgery. *Canadian Journal of Anaesthesia* 1991; **38**: 441–444.
10. Korttila K. The study of postoperative nausea and vomiting. *British Journal of Anaesthesia* 1992; **69** (Suppl. 1): 20S–23S.
11. Comroe JH, Dripps RD. Reactions to morphine in ambulatory and bed patients. *Surgery, Gynecology and Obstetrics* 1948; **87**: 221–224.
12. Gutner LB, Gould WJ, Batterman RC. The effects of potent analgesics upon vestibular function. *Journal of Clinical Investigation* 1952; **31**: 259–266.
13. Brandt Th, Paulus W, Straube A. Vision and posture. In: Bles W, Brandt Th, eds. *Disorders in Posture and Gait.* Amsterdam: Elsevier, 1986; 157–175.
14. Pyykkö I, Schalen L, Matsuoka I. Transdermally administered scopolamine vs. dimenhydrinate, II effect on different types of nystagmus. *Acta Otolaryngologica (Stockholm)* 1985; **99**: 597–604.
15. Honkavaara P, Hovorka J, Korttila K. Nausea and vomiting after gynaecological laparoscopy depends upon the phase of the menstrual cycle, *Canadian Journal of Anaesthesia* 1991; **38**: 876–879.
16. Hiller A, Pyykkö I, Saarnivaara L. Evaluation of postural stability by computerised posturography following outpatient paediatric anaesthesia. Comparison of propofol/alfentanil/N_2O anaesthesia with thiopentone/halothane/N_2O anaesthesia. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 556–561.
17. Aalto H, Pyykkö I, Starck J. Computerized posturography, a development of the measuring system. *Acta Otolaryngologica (Stockholm)* 1988; **449**: 71–75.
18. Ishizaki H, Pyykkö I, Aalto H, Starck J. Repeatability and effect of instruction of body sway. *Acta Otolaryngologica (Stockholm)* 1991; Suppl. **481**: 589–592.
19. Rabey PG, Smith G. Anaesthetic factors contributing to postoperative nausea and vomiting. *British Journal of Anaesthesia* 1992; **69** (Suppl. 1): 40S–45S.
20. Mitchelson F. Pharmacological agents affecting emesis, a review (part I). *Drugs* 1992; **43**: 295–315.

21. Young R, Sun DCH. Effect of glycopyrrolate on antral motility, gastric emptying and intestinal transit. *Annals of New York Academy of Sciences* 1962; **99**: 174–178.
22. Mitchelson F. Pharmacological agents affecting emesis, a review (part II). *Drugs* 1992; **43**: 443–463.
23. Reason JT, Brand JJ. *Motion Sickness*. London: Academic Press, 1975; 256–262.
24. Purkis IE. Factors that influence postoperative vomiting. *Canadian Anaesthetists Journal* 1964; **11**: 335–353.
25. Kamath B, Curran J, Hawkey C, Beattie A, Gorbutt N, Guiblin H, Kong A. Anaesthesia, movement and emesis. *British Journal of Anaesthesia* 1990; **64**: 728–730.
26. Larijani GE, Gratz I, Afshar M. Postoperative nystagmus and nausea. *Annals of Pharmacotherapy* 1994; **28**: 179–181.

British Journal of Anaesthesia 1996; **76**: 54–60

Single dose i.v. tropisetron in the prevention of postoperative nausea and vomiting after gynaecological surgery

V. CAPOUET, C. DE PAUW, B. VERNET, D. IVENS, V. DERIJCKE, L. VERSICHELEN, H. VAN AKEN, B. ICKX, L. RITTER AND F. HULSTAERT

Summary

In a prospective, randomized, multicentre, double-blind, placebo-controlled study, we have compared the efficacy of a single i.v. dose of tropisetron 0.5 mg, 2 mg and 5 mg in the prevention of postoperative nausea and vomiting (PONV). We studied 385 ASA class I and II female patients undergoing abdominal or vaginal gynaecological surgery, including laparoscopy. Tropisetron or placebo were administered before a standardized general anaesthetic. The frequency of vomiting in the 24-h period after entry into the recovery room was reduced from 44% after placebo to 31%, 26% and 30% after tropisetron 0.5 mg, 2 mg and 5 mg, respectively ($P = 0.06$, $P = 0.009$ and $P = 0.043$; unadjusted). Compared with placebo, nausea was reduced from 55% to 46%, 34% and 46% ($P = 0.25$, $P = 0.003$, $P = 0.22$), and need for rescue treatment from 39% to 29%, 23% and 35% ($P = 0.13$, $P = 0.017$ and $P = 0.59$) for the same groups. Tropisetron 2 mg appeared to be the optimal dose for prophylaxis against PONV with a side-effect profile similar to that of placebo. (*Br. J. Anaesth.* 1996; **76**: 54–60)

Key words

Vomiting, nausea. Vomiting, antiemetics. Serotonin antagonist, tropisetron.

Postoperative nausea and vomiting (PONV) remain among the most common of anaesthesia-related adverse effects [1]. The aetiology of PONV is multifactorial and includes factors related to the characteristics of the patient, the type of surgery, type of anaesthetic and postoperative factors [2–5]. Antiemetic prophylaxis may be justified in patients who are at greater risk of developing postoperative nausea and/or vomiting [2]; these include patients with a history of previous postoperative emesis and women undergoing gynaecological procedures, e.g. laparoscopy.

Antiemetics with an antidopaminergic action such as metoclopramide and droperidol are often used in the control of PONV but their use is limited by side-effects including sedation, hypotension, extrapyramidal symptoms and dysphoria [6].

Tropisetron (Navoban, ICS 205-930, Sandoz Pharma Ltd, Switzerland) is a selective competitive 5-HT_3 receptor antagonist, which has low affinity for 5-HT_4 receptors [7] and little or no activity at the non-5-HT_3 receptors, such as α_1, α_2 and β_1 adrenoceptors, muscarinic and nicotinic cholinergic receptors, histamine H_1 and H_2 receptors and dopamine D_2 receptors [8]. At a dose of 5 mg once daily, tropisetron has been shown to be an effective and well tolerated agent for the prevention of chemotherapy-induced emesis [9]. The metabolism of tropisetron in humans is linked to the polymorphically expressed cytochrome *P-450* IID6 enzyme system. The elimination half-life of tropisetron is 8 h in fast metabolisers and even longer in slow metabolisers [10], which could make this agent suited to prevention of PONV using a single dose. A single i.v. dose of tropisetron 5 mg has been shown to reduce significantly the incidence of PONV after gynaecological surgery under general anaesthesia [11]. The aim of the present study was to determine if smaller doses of tropisetron would be effective compared with placebo in the prevention of PONV.

Patients and methods

This randomized, multicentre, placebo-controlled, double-blind study was carried out in eight hospitals in Belgium and was conducted with the approval of the local Ethics Committees. The study was explained to each patient and written or oral witnessed informed consent was obtained. We studied ASA grade I and II women, between 18 and 75 yr, undergoing abdominal or vaginal gynaecological surgery, including laparoscopy, under general anaesthesia. Patients were expected to remain in hospital for at least 6 h after surgery. Patients were excluded if they had vomited during the 24 h before surgery or if they had received antiemetics during

---

V. CAPOUET*, MD, Centre Hospitalier Universitaire Vésale, Montigny-le-Tilleul. C. DE PAUW, MD, Heilig Hartkliniek, Eeklo. B. VERNET, MD, Cliniques Universitaires Saint-Luc, Brussels. D. IVENS, MD, Akademisch Ziekenhuis VUB, Brussels. V. DERIJCKE, MD, Algemeen Ziekenhuis Heilige Familie, Ghent. L. VERSICHELEN, MD, Universitair Ziekenhuis Gent, Ghent. H. VAN AKEN, MD, PHD, Universitair Ziekenhuis Gasthuisberg, Leuven. B. ICKX, MD, Hôpital Erasme, Brussels. L. RITTER, MS, International Institute for Drug Development, Brussels. F. HULSTAERT, MD, MSC, Sandoz Pharma, Brussels, Belgium. Accepted for publication: August 14, 1995.

*Address for correspondence: Department of Anaesthesiology, CHU Vésale, Route de Gozée 706, B-6110 Montigny-le-Tilleul, Belgium.

the same period. Patients were also excluded if they were expected to have a nasogastric tube after surgery, if they had a history of alcohol or drug abuse, if they were known to have hypersensitivity reactions, or if they were pregnant or lactating with the exception of those undergoing termination of early pregnancy combined with laparoscopic tubal ligation. Baseline information included height, weight, age, ethnic origin and days since start of last menstrual cycle. The current and past medical history of the patient was also recorded with special attention paid to motion sickness or PONV after general anaesthesia.

Patients were allocated randomly to one of the four treatment groups using a block size of 12 per centre. The study medication consisted of 5 ml ampoules containing 5 mg of tropisetron or perfectly matching placebo ampoules and was supplied to the centres in a sealed box containing a leaflet with instructions for preparation. The randomization number was printed on the box. A 5-ml syringe was prepared by the local pharmacist (in four centres) or a physician or nurse not participating in the study in any other way. In accordance with the instructions on the leaflet in the medication box 0.5 ml, 2 ml or 5 ml were obtained from the study ampoule and diluted with normal saline to a total volume of 5 ml. The double-blind character of the study was further assured by also having the three possible procedures performed for placebo.

The contents of the 5-ml syringe were then administered i.v. over 1 min before the start of induction of anaesthesia. Vital signs (systolic and diastolic arterial pressure and heart rate) were recorded immediately before, and 1 min after injection of the drug and 1 min after the start of induction.

Premedication was standardized at each centre and consisted of diazepam, alprazolam, lormetazepam or no premedication. All patients underwent tracheal intubation and received general anaesthesia including an induction agent (thiopentone), an opioid (fentanyl or sufentanil), and nitrous oxide supplemented with isoflurane. Neuromuscular block was facilitated with atracurium or vecuronium and reversed as appropriate with an anticholinesterase (neostigmine) with glycopyrrolium as the recommended anticholinergic agent. The choice of the opioid and the neuromuscular blocker was also standardized at each centre. The use of a nasogastric tube during surgery was allowed if removed by the end of the operation.

The duration of anaesthesia and the awakening time, i.e. the time between the end of administration of anaesthesia and the time of eye opening on request, were recorded with the level of consciousness after 30 min in the recovery room. The occurrence of emetic episodes in the operating room was also recorded. Postoperative analgesia was standardized. Patients could receive propacetamol, paracetamol or piritramide, an opioid analgesic. If the patient experienced PONV, the choice of the rescue treatment was at the discretion of the investigator. The first routine measurement of heart rate and systolic and diastolic arterial pressure after arrival in the ward was also recorded. In a single centre, electrocardiographic (ECG) recordings were obtained before surgery (baseline ECG), and 2 h (2-h ECG), 4 h (4-h ECG) and 24-h (24 h ECG) after administration of the study drug. Patients at that centre stayed in the recovery room for the 2-h and 4-h ECG.

In agreement with a study using a similar design [12] the main 24-h evaluation period for nausea and emesis began after the patient entered the recovery room and was capable of responding to a verbal command. This 24-h period was divided further into three assessment periods. The first period corresponded to the stay in the recovery room. The second period started when the patient left the recovery room and ended when 6 h of the 24-h period had passed. The third period covered the next 18 h. For the purpose of data collection no distinction was made between vomiting and retching. An emetic episode was defined as a single vomit or retch, or multiple vomits or retches separated in time by less than 1 min. Presence or absence of nausea was also recorded together with rescue treatment, if given. The patients were given diary cards on which to record the occurrence of emetic episodes, nausea and administration of antiemetic drugs. For the assessment of safety and efficacy the investigator used the patient's diary card and the observations of the nursing staff and questioned the patient directly. Day-case surgery patients remained in hospital during the first two assessment periods and were questioned by phone at the end of the 24-h observation period. In addition, a diary card completed by the patient was sent by mail to the study centre. Day-case surgery patients could be enrolled only in those centres where follow-up for the 6–24-h period could be guaranteed by the investigator.

ENDPOINTS AND STATISTICAL ANALYSIS

The primary efficacy variable of the study was the proportion of patients defined by the presence or absence of any emetic episodes over the 24-hour period regardless of rescue treatment given. A minimum sample size of 360 patients in four groups of 90 patients was selected to detect a 50 % reduction in the frequency of emetic episodes, from 40–50 % with placebo to 20–25 % with the optimal dose of tropisetron at the 5 % significance level with 80 % power. No interim analyses were planned or conducted.

For the primary efficacy variable the differences in proportions between treatment groups were tested by means of chi-square tests without continuity correction. A global test of all treatment groups against placebo was followed by pairwise tests comparing placebo with each dose of tropisetron. A closed-test procedure was used in order to ensure that the nominal level of significance was kept at 0.05 [13]. All tests were two-sided. Statistical analyses were performed using SAS version 6.08 under licence from SAS Institute (Cary, NC, USA).

Both the adjusted P values obtained using this closed test procedure and the unadjusted P values are reported. Secondary efficacy variables were the occurrence of nausea over the 24-h postoperative period, the administration of rescue treatment over the same period and the occurrence of emetic episodes over the 24-h period including events in the operating room. P values of the comparisons based on these secondary efficacy variables are reported with the caveat that their significance level must be adjusted to account for multiple testing.

Further exploratory analyses of possible prognostic factors were performed using logistic regression models. The following factors were considered: treatment group, centre, age, weight, history of PONV, motion sickness, days since last menses (< 8, 8–40, $\geqslant 40$ days), use of a benzodiazepine as premedication, type of surgery (laparoscopy, laparotomy), duration of anaesthesia, use of an anticholinergic before or during anaesthesia, use of postoperative opioids, and use of rescue treatment for nausea. Each factor was considered alone in the model, and then the final model was built by taking the most significantly related factor and adding the remaining factors not yet in the model until all significantly related factors had been included. The odds ratio and 95 % confidence intervals (CI) were calculated for the variables in the final model, both unadjusted, and adjusted for the other factors.

Results

CHARACTERISTICS OF THE PATIENTS AND THE ANAESTHESIA

Informed consent was obtained and study medication was prepared for a total of 391 sequential patients. The number of patients enrolled per centre varied between 33 and 70. Three patients withdrew their consent before administration of the study drug. Three ineligible patients were withdrawn from the study before administration of study medication because of a history of angioneurotic oedema, an ovarian carcinoma with metastases and a positive pregnancy test. The study medication was administered to a total of 385 patients in the 1-h period before the start of induction. In a single patient, induction followed 125 min after study drug administration because of unexpected delay in the surgery schedule. All 385 female patients were included in the analysis.

In this study 381 of 385 patients (99 %) were white. The groups were comparable in age, weight, height, days since last menstrual cycle and proportion of patients with a history of general anaesthesia and PONV or motion sickness (table 1).

The mean time between administration of study drug and the start of induction was 9 min and this was similar for all groups. In all four groups laparoscopy was the most common type of surgery (in 56 % of the patients), followed by abdominal hysterectomy (table 2).

Benzodiazepine premedication was administered to 72 % of all patients with the majority of these (60 %) receiving diazepam. Other benzodiazepines given included alprazolam (21 %), lormetazepam (16 %), midazolam (2 %) and lorazepam (in one patient). The mean doses were similar for all groups (diazepam 8.5 mg, alprazolam 0.8 mg, lormetazepam 3.3 mg). Anticholinergic premedication was used in five (5 %), three (3 %), six (6 %) and six (6 %) patients in the placebo, tropisetron 0.5-mg, 2-mg and 5-mg groups, respectively, and consisted of glycopyrronium ($n = 15$, mean dose 0.2 mg) or atropine 0.3 mg ($n = 5$).

Table 1 Characteristics of the four groups (mean (range or SD) or number (%))

	Placebo	Tropisetron		
	($n = 97$)	0.5 mg ($n = 97$)	2 mg ($n = 95$)	5 mg ($n = 96$)
Age (yr)	41 (22–74)	38 (19–69)	38 (24–67)	41 (18–74)
Weight (kg)	66 (13)	63 (11)	66 (15)	65 (12)
Height (cm)	163 (7)	164 (6)	164 (6)	163 (7)
Days since last menstrual cycle	12.5	16.2	13.8	14.0
n	59	71	63	64
Motion sickness	14 (14 %)	19 (20 %)	10 (11 %)	8 (8 %)
Previous general anaesthesia	73 (75 %)	73 (75 %)	71 (75 %)	72 (75 %)
General anaesthesia with PONV	21 (22 %)	17 (18 %)	22 (23 %)	22 (23 %)

Table 2 Types of operations performed (number (%)). *Laparoscopic surgery included laparoscopic tubal ligation (15 % of all patients), dilatation and curettage with laparoscopic tubal ligation (5 %), diagnostic laparoscopy (10 %), laparoscopy for ovarian cyst (10 %), laser laparoscopy (6 %), repermeabilization of fallopian tubes (3 %), laparoscopy for endometriosis (3 %) or other (3 %)

	Placebo	Tropisetron		
	($n = 97$)	0.5 mg ($n = 97$)	2 mg ($n = 95$)	5 mg ($n = 96$)
Laparoscopic surgery*	52 (54 %)	58 (60 %)	55 (58 %)	49 (51 %)
Abdominal hysterectomy	21 (22 %)	17 (18 %)	17 (18 %)	14 (15 %)
Other gynaecological laparotomy	6 (6 %)	5 (5 %)	7 (7 %)	9 (9 %)
Vaginal hysterectomy	9 (9 %)	5 (5 %)	11 (12 %)	11 (11 %)
Other vaginal surgery	9 (9 %)	11 (11 %)	5 (5 %)	13 (14 %)
Breast surgery	0 (0 %)	1 (1 %)	0 (0 %)	0 (0 %)

Table 3 Anaesthetic duration, type of anaesthetic and postoperative opioids (mean (range)). *Time between start of induction and end of administration of anaesthetics. †Maximum end-tidal concentration

		Tropisetron		
	Placebo (*n* = 97)	0.5 mg (*n* = 97)	2 mg (*n* = 95)	5 mg (*n* = 96)
Anaesthetic duration (min)*	74 (17–229)	76 (21–177)	80 (24–281)	78 (15–207)
Induction agent				
Thiopentone i.v. (mg)	320 (150–500)	315 (175–500)	317 (150–500)	324 (150–600)
Neuromuscular blocker				
Atracurium i.v. (mg)	37 (20–110)	33 (10–85)	37 (15–130)	33 (10–90)
n	64	65	61	62
Vecuronium i.v. (mg)	7.5 (4–15)	7.2 (4.5–14)	7.4 (4–11.5)	7.5 (5–13)
n	33	31	34	34
Inhalation anaesthetic				
Nitrous oxide (%)	57 (40–70)	57 (40–66)	56 (40–66)	56 (30–66)
Isoflurane† (%)	0.9 (0.1–2)	0.9 (0.4–1.5)	0.9 (0.2–1.5)	1.0 (0.2–2)
Opioids during operation				
Fentanyl i.v. (µg)	326 (100–750)	284 (100–550)	286 (100–550)	293 (100–1100)
n	44	45	43	42
Sufentanil i.v. (µg)	16.8 (5–40)	15.5 (5–33)	17.9 (5–50)	18.2 (5–50)
n	53	52	53	54
Opioids in recovery room				
Piritramide i.m. (mg)	14.9 (2–35)	14.9 (2–20)	15.8 (8–23)	15.7 (4–40)
n	35	35	45	34
Piritramide i.v. (mg)	5.3 (2–10)	5.3 (1–12)	3.7 (1–6)	5.8 (2–16)
n	18	15	14	6
Opioids on ward				
Piritramide i.m. (mg)	18.9 (10–40)	22.0 (10–60)	19.4 (8–40)	22.3 (10–60)
n	27	29	29	32

Table 4 Results for the primary and secondary efficacy variables in 24-h postoperative period for each treatment group (number (%)). **P* value for comparison with placebo (adjusted *P* value)

		Tropisetron		
	Placebo (*n* = 97)	0.5 mg (*n* = 97)	2 mg (*n* = 95)	5 mg (*n* = 96)
Primary				
Patients with emesis	43 (44 %)	30 (31 %) 0.06* (0.06)	25 (26 %) 0.009* (0.009)	29 (30 %) 0.043* (0.043)
Secondary				
Patients with emesis (including operating room)	43 (44 %)	31 (32 %) 0.08* (0.08)	28 (29 %) 0.033* (0.033)	32 (33 %) 0.12* (0.12)
Patients with nausea	53 (55 %)	45 (46 %) 0.25* (0.25)	32 (34 %) 0.003* (0.03)	44 (46 %) 0.22* (0.22)
Patients with rescue treatment	38 (39 %)	28 (29 %) 0.13* (0.23)	22 (23 %) 0.017* (0.09)	34 (35 %) 0.59* (0.59)

The duration of anaesthesia (overall mean 77 min), the use of anaesthetics and postoperative opioids are detailed in table 3. All patients had induction of anaesthesia with thiopentone and received nitrous oxide supplemented with isoflurane. Atracurium or vecuronium was used as neuromuscular blocking agent. One patient undergoing breast surgery did not receive a neuromuscular blocker. In 111 patients (29 %) the neuromuscular blocking agent was antagonized using neostigmine at a mean dose of 1.6 mg, in all but two patients associated with an anticholinergic agent consisting of glycopyrronium (*n* = 102, mean dose 0.4 mg) or atropine (*n* = 7, mean dose 0.3 mg). All patients received opioids during anaesthesia and these consisted of sufentanil (in 55 %) or fentanyl. One patient received both agents. Opioids were antagonized using naloxone (mean dose of 73 µg) in four (4 %), five (5 %), two (2 %) and five (5 %) patients in the placebo, tropisetron 0.5-mg, 2-mg, and 5-mg groups, respectively. Postoperatively, opioids were given to approximately 70 % of the patients in each of the groups and consisted primarily of piritramide. Pethidine was used for three patients. Other postoperative analgesics consisted of propacetamol or paracetamol. Intraoperative bradycardia was treated with atropine in eight patients (mean dose 0.4 mg) and with glycopyrronium in seven patients (mean dose 0.4 mg). Eleven patients (3 %) received a gastric tube during anaesthesia.

The patients stayed in the recovery room for a mean of 140 min. Patients having day-case surgery

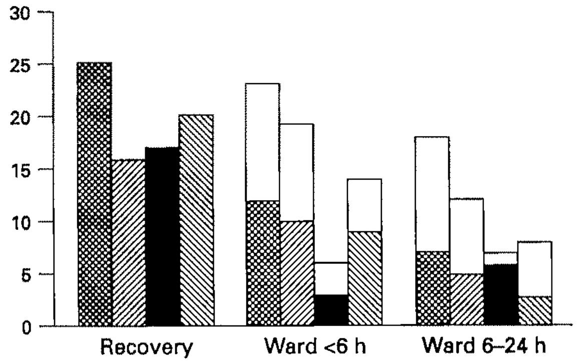


Figure 1 Percentage of patients with a first occurrence of emesis (first block) and percentage of patients with recurrence of emesis that started in a previous period (blank bars stacked on top) by assessment period in the placebo (▩) and tropisetron 0.5 mg (▨), 2 mg (■) and 5 mg (▧) groups.

represented 6 % of all patients (22 of 385) and were distributed evenly over the four treatment groups. All other patients remained in hospital for the full 24-h observation period.

EFFICACY RESULTS

In one patient the efficacy could not be assessed because of postoperative intragastric suction following intraoperative perforation of the intestinal wall by a laparoscope. The results for the primary endpoint and the secondary endpoints are listed in table 4. Both tropisetron 2 mg and 5 mg resulted in significant reduction in the incidence of vomiting compared with placebo. Vomiting or retching when the patient was still in the operating room after surgery occurred in three (3 %), three (3 %), three (3 %) and seven patients (7 %) in the placebo, tropisetron 0.5-mg, 2-mg and 5-mg groups respectively. When this incidence of vomiting is included in the 24-h period results, a significant decrease compared with placebo occurred only for the 2-mg dose. Compared with placebo the reduction in incidence of nausea and the use of rescue treatment were also significant for the 2-mg dose but not for the other doses of tropisetron tested.

Rescue treatment was administered to 19 % of all patients in the recovery room and to 18 % of all patients on the ward and consisted most frequently of alizapride (50 mg to 250 mg i.v.), followed by metoclopramide (10 mg to 40 mg i.v.). Six patients received droperidol 1.25 mg i.v. The mean doses of these agents given in the recovery room and on the ward were similar for all groups.

The frequency of first emetic episodes per assessment period are presented in figure 1, together with the frequency of recurrences of emesis that had started in a previous period. Fewer recurrences were seen in the second and third period for both the tropisetron 2-mg and 5-mg groups whereas the effect on first occurrence of vomiting in the first, second and third observation period was most pronounced for the tropisetron 0.5-mg, 2-mg and 5-mg doses, respectively.

The analysis of the subgroup of patients with a positive history of PONV revealed a frequency of vomiting in the placebo treatment group of 71 % (15 of 21 patients), which was reduced to 44 % (7 of 16 patients), 36 % (8 of 22 patients) and 41 % (9 of 22 patients) for the 0.5-mg, the 2-mg and the 5-mg doses, respectively. Furthermore, the subgroup analyses based on the use of a benzodiazepine as premedication, the duration of anaesthesia, the type of surgery, the presence or absence of motion sickness, the number of days since last menses, the use of an anticholinergic before or during anaesthesia and the use of postoperative opioids suggested that the efficacy of tropisetron was not restricted to a single subgroup.

The prognostic factors were included in a logistic model to find which ones were related most significantly to the primary outcome variable. The factors treatment, previous PONV and motion sickness were significant in the univariate models. The only factors which remained significant when considering combinations of factors were treatment, previous history of PONV and use of anticholinergics. There were no significant interactions. The adjusted odds ratio (95 % CI) of treatment compared with placebo were 0.53 (0.29, 1.0), 0.40 (0.21, 0.76) and 0.51 (0.27, 0.95) for tropisetron 0.5 mg, 2 mg and 5 mg, respectively. The adjusted odds ratio (95 % CI) associated with previous PONV was 2.41 (1.43, 4.07) and with use of anticholinergics 0.53 (0.32, 0.87).

SAFETY RESULTS

The recovery from anaesthesia measured by the waking time and the level of consciousness assessed 30 min after arrival in the recovery room was very similar in all four groups (table 5). All adverse events

Table 5 Recovery from anaesthesia (mean; median (range) or number (%)). *Time between end of administration of anaesthetics and eye opening on request

		Tropisetron		
	Placebo ($n = 97$)	0.5 mg ($n = 97$)	2 mg ($n = 95$)	5 mg ($n = 96$)
Waking time (min)*	12.3	11.9	12.6	13.9
	10 (2–75)	12 (1–40)	12 (2–32)	13 (3–50)
Level of consciousness 30 min after arrival in recovery				
Awake	75 (77 %)	82 (85 %)	78 (82 %)	76 (79 %)
Reacts to verbal command	19 (20 %)	14 (14 %)	16 (17 %)	20 (21 %)
Reacts to physical stimuli	2 (2 %)	1 (1 %)	1 (1 %)	0 (0 %)
Not arousable	1 (1 %)	0 (0 %)	0 (0 %)	0 (0 %)

Table 6 Number of adverse events. *Not all cases of bradycardia treated with an anticholinergic (number in brackets) were reported as an adverse event

		Tropisetron		
	Placebo ($n = 97$)	0.5 mg ($n = 97$)	2 mg ($n = 95$)	5 mg ($n = 96$)
Events during anaesthesia:				
Difficulty in intubation	0	0	0	1
Rash during induction	1	1	0	2
Allergic reaction during induction	0	1	0	0
Wheezing at expiration	1	0	0	0
Hypertension	1	1	2	1
Bradycardia*	1 (5)	1 (3)	0 (4)	2 (3)
Intestinal perforation	0	1	0	0
Uterine haemorrhage	1	0	0	0
Uterine perforation	0	1	0	0
Postoperative events:				
Headache	1	2	2	4
Dizziness	1	1	0	2
Hypotension	0	0	0	1
Hyperventilation	1	0	0	0
Haematemesis	1	0	0	0
Stomach ache	1	0	0	0
Pruritus	1	0	0	0
Eczema	0	1	0	0
Local allergic reaction (skin)	0	1	0	0
Eye irritation	0	0	1	0
All adverse events:				
Patients with adverse events	10 (10%)	11 (11%)	5 (5%)	12 (13%)

are listed in table 6. There were no allergic reactions or other adverse events in the period between study drug administration and start of induction of anaesthesia. Most adverse events occurred only once. With perhaps the exception of headache, there was no increased frequency of adverse events in patients who received a higher dose of tropisetron.

Intraoperative bradycardia, reported as adverse event or treated with an anticholinergic, did not occur more frequently in any of the tropisetron groups compared with placebo, nor did heart rate, systolic and diastolic arterial pressure show a differential pattern of response to the anaesthesia for the four study groups. There were five cases of intraoperative hypertension documented as adverse event, distributed over all treatment groups, and one case of postoperative hypotension, which occurred 12 h after administration of tropisetron 5 mg in a patient suffering from severe nausea.

Four ECG recordings per patient were obtained in a single centre for 47 patients. There were no ECG abnormalities other than a single case of a transient first degree AV block and a transient QTc prolongation in another patient, both observed in the immediate postoperative period. The patient showing a transient first degree AV block already had a PQ/PR interval at baseline of 0.18 s after a history of complete thyroidectomy for Hashimoto thyroiditis with treatment-resistant hyperthyroidism. This patient had received tropisetron 2 mg. The patient with the transient prolongation of the QTc for the 2-h ECG and the 4-h ECG had received tropisetron 0.5 mg and had a 'double hump' aspect of the T wave at baseline.

Discussion

In accordance with the recommendations published by Korttila [14] we conducted a double-blind, placebo-controlled, comparative study with a sample size large enough to detect small differences and permit an even distribution of confounding factors that affect emesis among the study groups.

Our data show that a single dose of tropisetron 2 mg was effective in the prophylaxis of PONV and that the results for the high-risk subgroup of patients with a positive history of PONV are consistent with the overall results. Both tropisetron 2 mg and 5 mg resulted in a significant reduction in vomiting compared with placebo for the main 24-h period. The differences between the results for the three doses of tropisetron were, however, not large. For practical reasons and given the wide therapeutic index of tropisetron, the traditional population-based approach to dose selection was used in this study. Larger differences between the doses of tropisetron tested would perhaps have indicated a clearer dose response relationship.

Although the numbers are small, the retching and vomiting associated with the removal of the tracheal tube in the operating room at the end of anaesthesia was clearly not suppressed by tropisetron. As more of these events occurred in the 5-mg dose group, the difference between placebo and the 5-mg dose was non-significant when these events were added to the main 24-h results (table 4). Figure 1 suggests that the efficacy of tropisetron was sustained beyond the first 6 h after surgery. This is in agreement with the relatively long half-life of tropisetron and supports the use of a single dose of tropisetron to cover the full 24-h period.

5-HT$_3$ receptor antagonists are not general antiemetics. Although 5-HT_3 receptor antagonists are beneficial in abdominal procedures, because these procedures may release 5-HT and activate visceral afferent pathways or the area postrema in a similar way to that proposed for anticancer therapies, it has been suggested that 5-HT_3 antagonists might be less effective in ear, nose and throat or ocular surgery [15]. Clinical trials with tropisetron are required to test this hypothesis.

As PONV is a multifactorial problem we have used logistic regression models to estimate factors predictive of response. Of interest was the composition of the final logistic regression model, in which use of an anticholinergic was retained as associated with a lower incidence of PONV, independent of the effect of tropisetron and thus suggesting that the combination of both type of drugs could be more effective in preventing PONV than each drug alone.

In this study we administered tropisetron before induction in the hope of blocking the effect of serotonin released during surgery. This is in contrast with a previous study [11] where tropisetron was administered shortly before wound closure, when most of the serotonin that activates the receptors, implicated in nausea and vomiting reflexes, may already have been liberated. In retrospect, and considering that the anaesthetic technique used was not identical in the two studies, the timing of administration of tropisetron did not seem to be a major determinant of efficacy.

Dose comparative studies in the prevention of PONV have been reported for ondansetron [12] and recently also for granisetron [16], two other 5-HT_3 antagonists. These studies were also conducted mainly in female patients undergoing abdominal gynaecological surgery. As was the case for tropisetron in this study, the minimum dose of ondansetron and granisetron found to be effective for prevention of PONV was lower than the dose used in the setting of cancer chemotherapy. Although the frequency of emesis in the placebo group was slightly lower in our study compared with a study with ondansetron [12], the extent of reduction of PONV by both agents seemed to be of the same order of magnitude. As was reported for ondansetron [12], our data also suggest that the effect of 5-HT_3 antagonists on vomiting might be more pronounced than the effect on nausea, which is not necessarily a low-level stimulation of the vomiting reflex. Nausea is also more difficult to assess than vomiting in the postoperative period. As PONV is a multifactorial problem, only correctly designed comparative studies allow for direct comparison of efficacy and safety of other 5-HT_3 antagonists with tropisetron.

In this study there are few adverse events. The cardiovascular events could be explained in the context of the anaesthesia and the surgery and did not indicate a dose-relationship or a cardiovascular effect different from placebo. The asymptomatic and transient ECG findings in the immediate postoperative period consisting of a single case of a first degree AV block and a prolonged QT interval in another patient may be explained by the patient condition and the anaesthesia [17, 18].

Acknowledgements

We thank following investigators and co-investigators: P. Baele, MD, PhD, E. Balatoni, MD, F. Camu, MD, PhD, F. Christiaens, MD, M. Coppens, MD, W. De Groote, MD, L. Deruyck, MD, A. d'Hollander, MD, PhD, A. Dubois, MD, E. Gilbart, MD, M. Nulens, MD, P. Pendeville, MD, G. Rolly, MD, PhD, M. Van Boven, MD, B. Vangehuchten, MD. We are also indebted to K. de Bruyn, MD, PhD and P. De Keyser, MD for critical scientific review. We further thank I. De Kerpel, MSc for data monitoring, to Ms A. Menten for study site coordination, to P. Baes, MSc, for data management, to P. Van Belle, MSc, for statistical support and to Ms S. Verbouwe for logistic support. The study was funded by Sandoz Pharma Ltd.

References

1. Dershwitz M. Advances in antiemetic therapy. *Anesthesiology Clinics of North America* 1994; **12**: 119–132.
2. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. *Anesthesiology* 1992; 77: 162–184.
3. Camu F, Lauwers H, Verbessem D. Incidence and aetiology of postoperative nausea and vomiting. *European Journal of Anaesthesiology* 1992; **9** (Suppl. 6): 25–31.
4. Lerman J. Surgical and patient factors involved in postoperative nausea and vomiting. *British Journal of Anaesthesia* 1992; **69** (Suppl. 1): 24S–32S.
5. Rabey PG, Smith G. Anaesthetic factors contributing to postoperative nausea and vomiting. *British Journal of Anaesthesia* 1992; **69** (Suppl. 1): 40S–45S.
6. Rowbotham DJ. Current management of postoperative nausea and vomiting. *British Journal of Anaesthesia* 1992; **69** (Suppl. 1): 46S–59S.
7. Hindle AT. Recent developments in the physiology and pharmacology of 5-hydroxytryptamine. *British Journal of Anaesthesia* 1994; 73: 395–407.
8. Seynaeve C, Verweij J, de Mulder PHM. 5-HT_3 receptor antagonists, a new approach in emesis: a review of ondansetron, granisetron and tropisetron. *Anti-Cancer Drugs* 1991; 2: 343–355.
9. Bruijn KM de. Tropisetron. A review of the clinical experience. *Drugs* 1992; **43** (Suppl. 3): 11–22.
10. Kutz K. Pharmacology, toxicology and human pharmacokinetics of tropisetron. *Annals of Oncology* 1993; 4 (Suppl. 3): S15–S18.
11. Zomers PJW, Langenberg CJM, de Bruijn KM. Tropisetron for postoperative nausea and vomiting in patients after gynaecological surgery. *British Journal of Anaesthesia* 1993; 71: 677–680.
12. Kovac A, McKenzie R, O'Connor T, Duncalf D, Angel J, Gratz I, Fagraeus I, McLeskey C, Joslyn AF. Prophylactic intravenous ondansetron in female outpatients undergoing gynaecological surgery: a multicentre dose-comparison study. *European Journal of Anaesthesiology* 1992; **9** (Suppl. 6): 37S–47S.
13. Budde M, Bauer P. Multiple test procedures in clinical dose finding studies. *Journal of the American Statistical Association* 1989; **84**: 792–796.
14. Korttila K. The study of postoperative nausea and vomiting. *British Journal of Anaesthesia* 1992; **69** (Suppl. 1): 20S–23S.
15. Andrews PLR. Physiology of nausea and vomiting. *British Journal of Anaesthesia* 1992; **69** (Suppl. 1): 2S–19S.
16. Fuji Y, Tanaka H, Toyooka H. Optimal anti-emetic dose of granisetron for preventing postoperative nausea and vomiting. *Canadian Journal of Anaesthesia* 1994; 41: 794–797.
17. Kaplan MM. The thyroid and the heart: how do they interact? *Journal of Cardiovascular Medicine* 1982; 7: 893–903.
18. Schmeling WT, Warltier DC, McDonald DJ, Madsen KE, Atlee JL, Kampine JP. Prolongation of the QT interval by enflurane, isoflurane, and halothane in humans. *Anesthesia and Analgesia* 1991; 72: 137–144.

British Journal of Anaesthesia 1996; **76**: 61–65

Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for Caesarean section

D. G. THOMAS, S. C. ROBSON, N. REDFERN, D. HUGHES AND R. J. BOYS

Summary

Thirty-eight healthy women undergoing elective Caesarean section under spinal anaesthesia at term were allocated randomly to receive boluses of either phenylephrine 100 μg or ephedrine 5 mg for maintenance of maternal arterial pressure. The indication for administration of vasopressor was a reduction in systolic pressure to ⩽ 90% of baseline values. Maternal arterial pressure (BP) and heart rate (HR) were measured every minute by automated oscillometry. Cardiac output (CO) was measured by cross-sectional and Doppler echocardiography before and after preloading with 1500 ml Ringer lactate solution and then every 2 min after administration of bupivacaine. Umbilical artery pulsatility index (PI) was measured using Doppler before and after spinal anaesthesia. The median (range) number of boluses of phenylephrine and ephedrine was similar; 6 (1–10) *vs* 4 (1–8) respectively. Maternal systolic BP and CO changes were similar in both groups, but the mean [95% CI] maximum percentage change in maternal HR was larger in the phenylephrine group (−28.5 [−24.2, −32.9]%) than in the ephedrine group (−14.4 [−10.6, −18.2]%). As a consequence atropine was required in 11/19 women in the phenylephrine group compared with 2/19 in the ephedrine group ($P < 0.01$). Mean umbilical artery pH [95% CI] was higher in the phenylephrine group (7.29 [7.28–7.30]) than in the ephedrine group (7.27 [7.25–7.28]). The results of the present study support the use of phenylephrine for maintenance of maternal arterial pressure during spinal anaesthesia for elective Caesarean section. (*Br. J. Anaesth.* 1996; **76**: 61–65)

Key words

Anaesthetic techniques, subarachnoid. Anaesthesia, obstetric. Complications, hypotension. Measurement techniques, Doppler ultrasound. Measurement techniques, echocardiography.

Hypotension can occur during spinal anaesthesia for Caesarean section despite fluid loading and adoption of the tilted supine position, with consequent risk of fetal acidaemia [1]. Ephedrine is considered the vasopressor of choice for treatment of hypotension although even prophylactic infusion of ephedrine does not reliably prevent maternal hypotension and fetal acidaemia [2].

Alpha-adrenergic agonists are an effective treatment of post-spinal hypotension but their use during pregnancy has been limited by concerns about uteroplacental blood flow (UPBF) [3, 4]. Two previous randomized studies have compared infusion of phenylephrine and ephedrine for prevention of post-spinal hypotension [5, 6]; no difference was found in umbilical artery pH between the groups, although Hall and colleagues [6] found that phenylephrine was less effective in maintaining systolic arterial pressure. Only one previous study has compared boluses of ephedrine or phenylephrine for treatment of post-spinal hypotension [7]. Phenylephrine was found to be equally effective as a vasopressor and its use was not associated with an increase in fetal acidaemia. However, maternal haemodynamic assessment was confined to measurement of arterial pressure.

Combined cross-sectional and Doppler echocardiography provides an accurate non-invasive method of measuring cardiac output (CO) in pregnancy [8, 9]. Doppler ultrasound can also be used to assess the fetal umbilical circulation and umbilical artery flow velocity waveform indices have been shown to be superior to cardiotocography in predicting fetal compromise [10]. It has been shown previously that changes in both of these variables, unlike changes in arterial pressure, correlate with umbilical artery pH at delivery [11].

The purpose of this study was to compare maternal and fetal haemodynamic changes, and umbilical artery pH, in subjects allocated randomly to receive phenylephrine or ephedrine for treatment of hypotension during spinal anaesthesia for elective Caesarean section.

Patients and methods

The study was approved by the Newcastle Health Authority and University of Newcastle-upon-Tyne Joint Ethics Committee. All subjects gave informed

---

DAVID G. THOMAS*, FFARCSI, Department of Anaesthesia, Dryburn Hospital, Durham. STEPHEN C. ROBSON, MD, MRCOG, Department of Obstetrics and Gynaecology, University of Newcastle-upon-Tyne. NANCY REDFERN, FRCA, DAVID HUGHES, FRCA, Department of Anaesthesia, RVI, Newcastle-upon-Tyne. RICHARD J. BOYS, PHD, FSS, Department of Statistics, University of Newcastle-upon-Tyne. Accepted for publication: 15 August 1995.

*Address for correspondence: Department of Anaesthesia, Dryburn Hospital, Durham DH1 5TW.

written consent. We studied 40 healthy women with an uncomplicated singleton pregnancy undergoing elective Caesarean section at term. The number of subjects was calculated to detect a difference in umbilical artery pH of 0.05 units as being significant at the 5 % level with 80 % power [12]. For the power calculation, we assumed a standard deviation of 0.05 pH units [13]. Randomization using opaque envelopes was performed by the pharmacy department which then issued coded 10-ml syringes containing either ephedrine 5 mg ml^{-1} or phenylephrine 100 µg ml^{-1}. Two subjects were excluded after randomization because of failure to obtain satisfactory Doppler waveforms. Characteristics of the 38 subjects studied are shown in table 1.

Each subject received oral ranitidine 150 mg on the evening before and on the morning of surgery. A volume of 30 ml sodium citrate 0.3 mol $litre^{-1}$ was given before induction of spinal anaesthesia. Ringer lactate solution 1500 ml was infused rapidly through a 14-gauge i.v. cannula and continued thereafter at a rate of approximately 10–15 ml min^{-1}. With patients in the sitting position 2.5 ml of bupivacaine 0.5 % with 8.0 % dextrose was given via a 24-gauge Sprotte needle at either L2-3 or L3-4. Immediately after administration of local anaesthetic solution the patient was placed in a full right lateral position for 2 min. The subject was then rolled transiently into full left lateral position before being placed in the left modified supine position until delivery. Dermatomal level of anaesthesia was assessed by thermal discrimination 15 min after induction of anaesthesia. Inspired air was supplemented with oxygen at 5 litre min^{-1} from induction of anaesthesia until clamping of the umbilical cord.

Arterial pressure was measured by an automated oscillometric technique (Accutor). Baseline systolic arterial pressure (SAP) was taken as the lowest of six readings during rest before induction of anaesthesia. After injection of local anaesthetic arterial pressure was measured at 1-min intervals. Whenever SAP decreased to less than 90 % of the baseline 1 ml of vasopressor was administered. Maternal heart rate was monitored using finger pulse oximetry. On each occasion that maternal heart rate decreased to below 60 min^{-1} atropine 0.3 mg i.v. was administered.

Maternal ascending aortic flow velocities were recorded in the left modified supine position using a 2 MHz continuous wave Doppler transducer (Doptek) placed in the suprasternal notch [8]. Recordings were made before and after fluid preloading, and then at 3, 5, 7, 9, 11, 13 and 15 min after administration of intrathecal bupivacaine. A spectral analyser performed fast Fourier transform analysis of the Doppler signal and the output was converted to velocity according to the Doppler equation. The angulation of the ultrasound beam was adjusted until the highest velocities with the least spectral dispersion were obtained; these were then stored in the computer memory and it was assumed that the recorded velocities were those at the aortic orifice and that the beam was parallel with flow. Heart rate (HR) and systolic velocity integral (area under the velocity curve) were calculated automatically by the computer. For the systolic velocity integral (SVI) calculations were made using 15/16 of the maximum frequency in order to exclude high-frequency artefacts. Minute distance (the product of HR and SVI) was averaged over 4–6 consecutive cardiac cycles. Systolic aortic annulus diameter was measured in the parasternal long axis plane using a 5-MHz cross-sectional transducer (Hewlett-Packard). Diameters were measured from the leading edge of the anterior wall to the leading edge of the posterior wall [8]. The average of three measurements before anaesthesia was used to calculate aortic cross-sectional area and this value was used for all calculations of cardiac output. Cardiac output was calculated as the product of minute distance and aortic cross-sectional area.

Umbilical artery flow velocity waveforms were measured using a 4-MHz continuous wave Doppler transducer [14]. Fast Fourier transform analysis of the Doppler signal was performed by a separate spectral analyser (Doptek). Fetal heart rate (FHR) and pulsatility index (PI), the difference between peak systolic and end diastolic velocities divided by the average velocity [15] were calculated automatically with the computer. The average of 4–6 consecutive cycles was used for each determination. Umbilical artery PI was measured before and then 15 min after spinal anaesthesia.

At delivery the umbilical cord was double-clamped and 1-ml samples of umbilical vein and artery blood obtained. Each sample was heparinized with 0.1 ml of heparin (1000 iu ml^{-1}) and acid/base analysis performed within 5 min of cord clamping (Radiometer ABL-30). Apgar scores at 1 and 5 min after delivery were recorded by the attending paediatrician, who was unaware of the vasopressor used.

STATISTICAL ANALYSIS

Differences between groups were compared using Student's *t*-test for normally distributed data, and the Mann-Whitney test for non-parametric data.

Table 1 Patient characteristics. Figures are means (95 % confidence intervals)

	Ephedrine	Phenylephrine
Maternal age (yr)	27.4 (25.3, 29.5)	30.0 (27.9, 32.1)
Maternal height (m)	1.61 (1.57, 1.65)	1.57 (1.54, 1.60)
Maternal weight (kg)	71.8 (67.3, 76.4)	71.0 (66.8, 75.2)
Gestational age (weeks)	38.7 (38.4, 39.0)	38.7 (38.3, 39.0)
Birth weight (kg)	3.27 (3.09, 3.45)	3.27 (3.07, 3.48)
Indication for Caesarean section:		
Breech presentation	4	2
Previous Caesarean section	15	17

Table 2 Maternal haemodynamic data. Figures are mean (95 % confidence intervals) or median (range)*. SAP = systolic arterial pressure)

	Ephedrine	Phenylephrine
Baseline SAP (mm Hg)	120 (114, 126)	126 (121, 131)
Maximum change in SAP (%)	−22.2 (−26.0, −18.4)	−23.1 (−27.3, −18.4)
Number of occasions on which SAP fell by > 20 %*	0 (0, 4)	0 (0, 6)
Number of boluses of vasopressor used*	4 (1, 8)	6 (1, 10)
Baseline cardiac output (litre min^{-1})	6.68 (6.21, 7.16)	6.34 (5.72, 6.97)
Cardiac output after preload (litre min^{-1})	7.95 (7.27, 8.64)	7.87 (7.08, 8.65)
Maximum change in cardiac output (%)	−5.6 (−10.2, −0.9)	−8.9 (−14.6, −3.1)
Baseline maternal heart rate (beat min^{-1})	87 (83, 91)	89 (83, 95)
Maximum change in maternal heart rate (%)	−14.4 (−18.2, −10.6)	−28.5 (−32.9, −24.2)
Subjects requiring atropine (HR < 60)	2	11

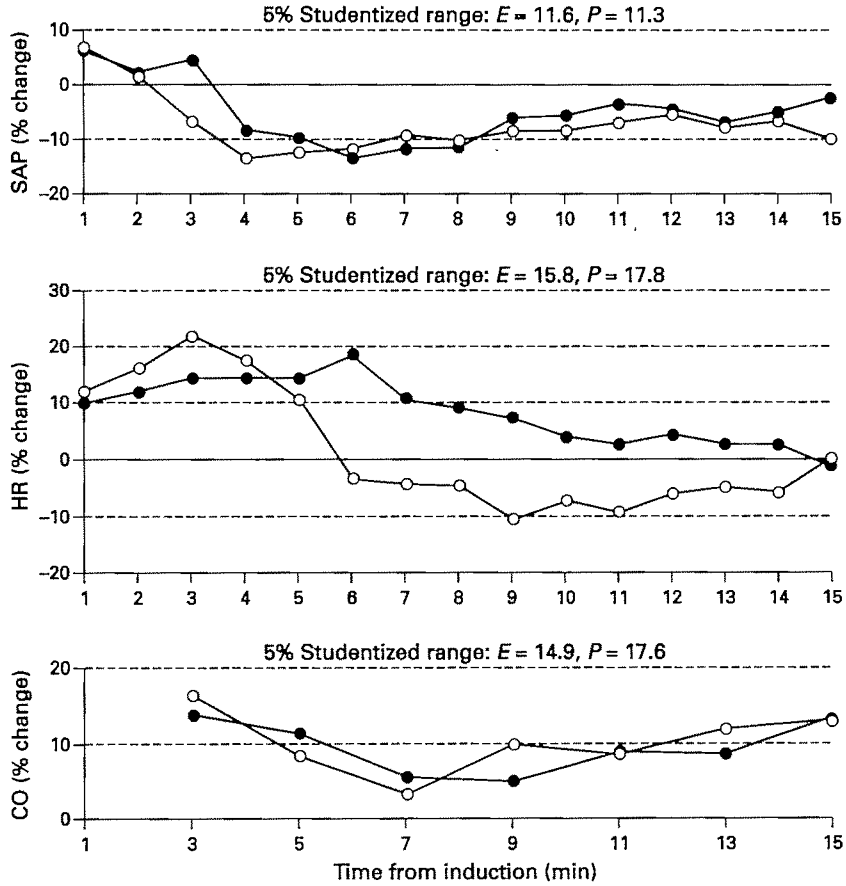


Figure 1 Mean percentage changes in systolic arterial pressure (SAP), heart rate (HR) and cardiac output (CO) from baseline values after induction of spinal anaesthesia in the ephedrine (●) and phenylephrine (○) groups, together with the respective Studentized ranges.

Comparison of proportions was performed using Fisher's exact test. Repeated measures analysis of variance was performed for each haemodynamic variable. To overcome the problem of multiple significance testing the differences between time points within the two groups were compared using the Studentized range at the 5 % level:

$$\text{Range} = q_{(v)} \times (s^2/\sqrt{n})$$

where $q_{(v)}$ = critical value for comparing two time points; s^2 = residual mean square with v degrees of freedom, n = number of subjects. The association between the number of doses of vasopressor and umbilical artery pH was assessed by Pearson's correlation coefficient. Results are presented as mean (95 % confidence interval), except where stated.

Results

Sensory block to T2–T4 was produced in all subjects by 20 min after injection of bupivacaine. There was no significant difference in the mean uterine incision to delivery (UD) interval in the two groups (ephedrine: median 72 [range 30–236] s, phenylephrine: median 57 [range 20–161] s). One subject in the ephedrine group had a UD interval of > 180 s, although the umbilical artery pH was normal (7.26).

Baseline haemodynamic measurements were similar in both groups (table 2). Cardiac output increased after fluid pre-loading in both groups. The maximum decrease in haemodynamic measurements, expressed as a percentage of the baseline value, is shown in table 2. Although there were no significant dif-

Table 3 Fetal data. Figures are mean (95% confidence interval)

	Ephedrine	Phenylephrine
Umbilical artery pulsatility index	0.84 (0.80, 0.88)	0.83 (0.78, 0.88)
Change in pulsatility index (%)	−0.8 (−2.4, +4.0)	+0.7 (−3.3, +4.8)
Fetal heart rate	135 (132, 138)	137 (134, 140)
Change in fetal heart rate (%)	+0.8 (−2.3, +3.8)	−4.3 (−7.4, −1.2)
Umbilical artery blood gases:		
pH	7.27 (7.25, 7.28)	7.29 (7.28, 7.30)
pCO_2 (kPa)	7.1 (6.8, 7.3)	6.7 (6.4, 6.9)
pO_2 (kPa)	2.5 (2.1, 2.8)	2.5 (2.2, 2.8)
HCO_3 (mmol litre^{-1})	23.4 (22.7, 24.1)	23.4 (22.8, 23.9)
BE (mmol litre^{-1})	−2.9 (−3.9, −1.9)	−2.0 (−2.6, −1.4)
Apgar < 7 at 1 or 5 min	0	0

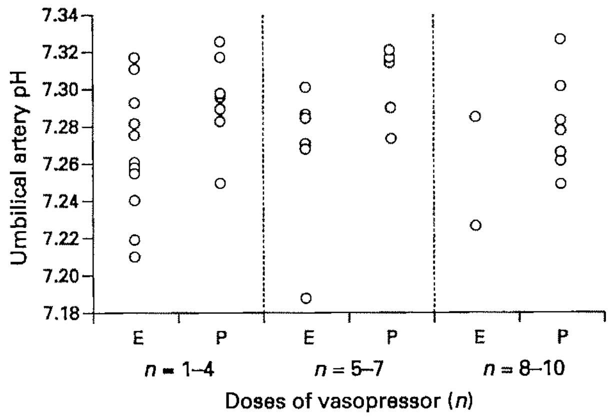


Figure 2 Effect of vasopressor use (number of doses of vasopressor given) on umbilical artery pH in the ephedrine (E) and phenylephrine (P) groups.

ferences in systolic pressure and CO, the maximum reduction in HR was greater in the phenylephrine group. As a result, more women required atropine (11/19, $P = 0.005$). The frequency of hypotension (SAP < 80% of baseline) and the requirement for vasopressor treatment was similar in the two groups (table 2).

The mean percentage changes in SAP, HR and CO after induction of spinal anaesthesia in the two groups, together with the respective Studentized ranges, are shown in figure 1. Systolic arterial pressure was reduced at 6–7 min in the ephedrine group, and at 4–6 min in the phenylephrine group. After an initial increase heart rate decreased in both groups. There was no significant change in cardiac output in either group.

Fetal data are presented in table 3. Umbilical artery pH was significantly higher in the phenylephrine group. Only one infant (in the ephedrine group) had an umbilical artery pH below 7.20. No apparent relationship was observed between umbilical artery pH and maximum percentage change in SAP (ephedrine $r = 0.08$, phenylephrine $r = 0.38$) or maximum percentage change in CO (ephedrine $r = 0.42$, phenylephrine $r = 0.15$). Baseline umbilical artery PI and fetal heart rate were comparable in the two groups. There was a small but statistically significant reduction in fetal heart rate in the phenylephrine group. No infants had Apgar scores of less than 7 at each time point.

The relationship between the number of doses of vasopressor required and umbilical artery pH is shown in figure 2. There was no significant correlation between the number of doses of either vasopressor and umbilical artery pH (ephedrine $r = -0.11$, phenylephrine $r = -0.22$).

Discussion

Hypotension is the most important complication of spinal anaesthesia and prompt effective treatment is considered essential to prevent fetal acidaemia. The results of the present study suggest that phenylephrine is as effective as ephedrine in restoring maternal arterial pressure during spinal anaesthesia and does not have detrimental effects on fetal haemodynamic state or umbilical artery pH. Although the incidence of maternal bradycardia was increased in women given phenylephrine there were no significant differences in maternal cardiac output between the two groups.

The present results confirm those reported in several previous studies [5–7] on the safety of phenylephrine in pregnancy. Alahuhta and colleagues [5] gave an initial bolus of ephedrine 5 mg or phenylephrine 100 μg when sensory analgesia had reached T5. This was followed by an infusion of 50 mg h^{-1} and 1000 μg h^{-1} respectively with further boluses if systolic arterial pressure decreased by 10 mm Hg from baseline. Although uteroplacental PI values increased following administration of phenylephrine (mean dose 488 (range 334–767) μg) there was no change in fetal heart rate or fetal Doppler indices. Umbilical artery pH was similar in both groups. Hall and colleagues [6] compared a prophylactic infusion of phenylephrine 10 μg min^{-1} with ephedrine 1 or 2 mg min^{-1} supplemented by 20-μg or 6-mg boluses respectively if systolic arterial pressure decreased by 20% from baseline. Although phenylephrine (mean dose 490 (range 300–680) μg) was less effective in maintaining systolic arterial pressure the umbilical artery pH was comparable in all three groups. Moran and colleagues [7] gave ephedrine 5–10 mg or phenylephrine 40–80 μg when systolic arterial pressure decreased by more than 5 mm Hg from baseline values. Boluses were repeated to maintain systolic arterial pressure above 100 mm Hg. Phenylephrine (total dose 335 (SD 31) μg) had similar vasopressor efficacy as that of ephedrine. The umbilical artery pH was significantly higher in the phenylephrine group.

At term the uterine vascular bed is maximally vasodilated and unable to autoregulate when perfusion pressure is reduced [16]. Consequently, a high adrenoceptor density renders uteroplacental blood flow (UPBF) potentially vulnerable to vasoconstriction induced by α-adrenergic agonists. Indeed, infusion of phenylephrine at 8 μg kg^{-1} min^{-1} has been reported to reduce ovine UPBF by 50 % [17]. However, the relationship between phenylephrine dose and uterine vascular resistance (UVR) is not linear and dramatic increases in UVR seem only to appear with doses greater than 100 μg min^{-1} [4]. Thus, the satisfactory fetal outcome in human studies may simply reflect the lower doses used, although it is worth noting that three women in the present study were given a total dose of 1000 μg phenylephrine. The umbilical artery pH values were 7.33, 7.30 and 7.25, the first being the highest in the whole study.

More than 50 % of women given phenylephrine in the current study developed significant bradycardia. A reduction in heart rate is a consistent effect in phenylephrine-treated women [5–7] although only Hall and colleagues [6] encountered bradycardia requiring treatment with atropine (heart rate < 40 min^{-1} in 2/10 subjects). Bradycardia could be caused by cardiac sympathetic denervation associated with high spinal block or a secondary baroreflex response to vasopressor-induced hypertension. In the current study there was no difference in extent of anaesthesia achieved. We were unable to find any relationship between either bradycardia or use of atropine and a hypertensive response to phenylephrine. This suggests that phenylephrine-associated bradycardia was caused by cardiac sympathetic denervation masked in the ephedrine group by the chronotropic effect of this β-adrenergic agonist.

Cardiac output was measured by combined Doppler and cross-sectional echocardiography. Values before and after fluid preloading are in close agreement with those published previously [11, 18]. In the present study initial aortic diameter measurements were used for all calculations of CO. We feel this is justified as aortic diameter is unlikely to change significantly during regional anaesthesia for Caesarean section [11, 18]. Umbilical artery Doppler waveforms were used to assess fetal wellbeing. In contrast with a previous study [11], we found no change in UAPI during spinal anaesthesia. Changes in previously normal umbilical artery waveform indices are generally associated with reductions in UPBF sufficient to cause fetal acidosis [19]. Thus the difference in UAPI results may reflect the lower UA pH in our earlier study.

Acknowledgements

David Thomas was supported by a research grant from the Northern Regional Health Authority. Doppler equipment was kindly loaned by Dr S. Hunter, Freeman Hospital, Newcastle-upon-Tyne and Mr J. Spencer, University College Hospital, London. Randomization and coding were performed by Mrs P. Sharma in the pharmacy department. This project could not have been completed without the help of our anaesthetic sister, Mrs M. Myles.

References

1. Corke BC, Datta S, Ostheimer GW, Weiss JB, Alper MH. Spinal anaesthesia for Caesarean section; the influence of hypotension on neonatal outcome. *Anaesthesia* 1982; **37**: 658–662.
2. Kang YG, Abouleish E, Caritis S. Prophylactic intravenous ephedrine infusion during spinal anesthesia for Cesearean section. *Anesthesia and Analgesia* 1982; **61**: 839–842.
3. Greiss FC, Crandell DL. Therapy for hypotension induced by spinal anaesthesia during pregnancy: observations on gravid ewes. *Journal of the American Medical Association* 1965; **191**: 89–92.
4. Magness RR, Rosenfeld CR. Systemic and uterine responses to α-adrenergic stimulation in pregnant and non-pregnant ewes. *American Journal of Obstetrics and Gynecology* 1986; **155**: 897–904.
5. Alahuhta S, Räsänem J, Joupilla P, Joupilla R, Hollmén AI. Ephedrine and phenylephrine for avoiding maternal hypotension due to spinal anaesthesia for caesarean section. *International Journal of Obstetric Anaesthesia* 1992; **1**: 129–134.
6. Hall PA, Bennett A, Wilkes MP, Lewis M. Spinal anaesthesia for caesarean section: comparison of infusions of phenylephrine and ephedrine. *British Journal of Anaesthesia* 1994; **73**: 471–474.
7. Moran DH, Perillo M, Bader AM, Datta S. Phenylephrine in treating maternal hypotension secondary to spinal anesthesia. *Journal of Clinical Anesthesia* 1991; **3**: 301–305.
8. Robson SC, Dunlop W, Moore M, Hunter S. Combined Doppler and echocardiographic measurement of cardiac output: theory and application in pregnancy. *British Journal of Obstetrics and Gynaecology* 1987; **94**: 1014–1027.
9. Easterling TR, Watts DH, Schmucker BC, Benedetti TJ. Measurement of cardiac output in pregnancy: validation of Doppler technique and clinical observations in pregnancy. *Obstetrics and Gynecology* 1987; **69**: 845–850.
10. Trudinger BJ, Cook CM, Jones L, Giles WB. A comparison of fetal heart rate monitoring and umbilical artery waveforms in the recognition of fetal compromise. *British Journal of Obstetrics and Gynaecology* 1986; **93**: 171–175.
11. Robson SC, Boys RJ, Rodeck C, Morgan B. Maternal and fetal haemodynamic effects of spinal and extradural anaesthesia for elective Caesarean section. *British Journal of Anaesthesia* 1992; **69**: 54–59.
12. Gore SM, Altman DG. How large a sample? *Statistics in Practice*. London: BMA publications, 1982: 6–8.
13. Yeomans ER, Hauth JC, Gilstrap LC, Strickland DM. Umbilical cord pH, PCO_2, and bicarbonate following uncomplicated term vaginal deliveries. *American Journal of Obstetrics and Gynecology* 1985; **151**: 798–800.
14. FitzGerald DE, Drumm JE. Non-invasive measurement of human fetal circulation using ultrasound: a new method. *British Medical Journal* 1977; **2**: 1450–1451.
15. Gosling RG, Dunbar G, King DH, Newman DL, Side CD, Woodcock JP, FitzGerald DE, Keates JS, MacMillan D. The quantitative analysis of occlusive peripheral vascular disease by a non-invasive ultrasonic technique. *Angiology* 1971; **22**: 52–55.
16. Greiss FC. Pressure-flow relationships in the gravid uterine vascular bed. *American Journal of Obstetrics and Gynecology* 1966; **96**: 41–47.
17. Greiss FC, Van Wilkes D. Effects of sympathomimetic drugs and angiotensin on the uterine vascular bed. *Obstetrics and Gynecology* 1964; **23**: 925–930.
18. Robson SC, Samsoon G, Boys RJ, Rodeck C, Morgan B. Incremental spinal anaesthesia for elective caesarean section: maternal and fetal haemodynamic effects. *British Journal of Anaesthesia* 1993; **70**: 634–638.
19. Copel JA, Schlafer D, Wentworth R, Belanger K, Kreitzer L, Hobbins JC, Nathanielsz PW. Does umbilical artery systolic/diastolic ratio reflect flow or acidosis? An umbilical artery Doppler study of fetal sheep. *American Journal of Obstetrics and Gynecology* 1990; **163**: 751–756.

British Journal of Anaesthesia 1996; **76**: 66–71

A double-blind comparison of 0.25% ropivacaine and 0.25% bupivacaine for extradural analgesia in labour

J. M. EDDLESTON, J. J. HOLLAND, R. P. GRIFFIN, A. CORBETT, E. L. HORSMAN AND F. REYNOLDS

Summary

Ropivacaine is a new aminoamide local anaesthetic. Compared with bupivacaine, ropivacaine possesses a higher threshold for systemic toxicity and a high selectivity for sensory fibres. We have compared prospectively these two agents in a concentration of 0.25% for extradural analgesia in labour. A total of 104 parturients requesting extradural analgesia were randomized to receive either ropivacaine or bupivacaine. The women in the bupivacaine group required more top-up doses to maintain analgesia (median 3.0 *vs* 2.0) ($P < 0.05$). The onset of sensory block, quality of analgesia, ultimate level of maximum sensory block and maternal satisfaction were similar in both groups. The incidence, intensity and duration of motor block were slightly but not significantly less in the ropivacaine group. The ropivacaine group had a higher incidence of spontaneous vaginal delivery (70.59% *vs* 52.00%). There was no significant difference in neonatal outcome as assessed by Apgar scores, umbilical acid–base status and neurological and adaptive capacity score at 2 and 24 h after delivery. We conclude that ropivacaine and bupivacaine in a concentration of 0.25% produced comparable analgesia for pain relief of labour with no detectable adverse effect on the neonate. (*Br. J. Anaesth.* 1996; **76**: 66–71)

Key words

Anaesthesia, obstetric. Anaesthetic techniques, extradural. Anaesthetics local, bupivacaine. Anaesthetics local, ropivacaine.

Extradural block is an effective means of providing analgesia in labour. However, all local anaesthetics used to date have significant disadvantages. For example, motor block results in decreased maternal mobility and satisfaction with the technique and may contribute to delay in the second stage of labour [1, 2] and postpartum backache [3]. Sympathetic block on the other hand may cause hypotension.

Serious maternal cardiotoxicity has been reported in the USA after inadvertent i.v. injection of bupivacaine [4]. Cardiac arrest, if it occurs, is resistant to treatment and has resulted in maternal deaths [5], although this has not been reported in the UK. In contrast, lignocaine is described as less cardiotoxic than bupivacaine [6]. Top-up doses are less likely to cause late decelerations in fetal heart rate [7] and its duration of action is shorter than that of bupivacaine. Repeated doses result in cumulative toxicity and tachyphylaxis. Scanlon and colleagues [8] suggested that lignocaine, administered extradurally, can result in the birth of "floppy but alert" babies (although his findings have been refuted by others) [7, 9, 10].

Recent attempts have been made to overcome these problems using either infusions of local anaesthetic rather than intermittent boluses [9, 11] or mixtures of dilute local anaesthetics with opioids [12–14]. There is no evidence of maternal benefit from using bupivacaine as the sole agent in extradural infusions and indeed extradural infusions of bupivacaine may result in more fetal heart rate decelerations than intermittent top-up doses [11].

Ropivacaine is a new aminoamide local anaesthetic with a structure closely related to bupivacaine and mepivacaine. Unlike bupivacaine (which is a racemic mixture), ropivacaine is a single enantiomer. It is the *S* isomer of *N*-propyl pipecholyl xylidine. Modern racemic local anaesthetics tend to be vasodilators at high and vasoconstrictors at lower concentrations. Ropivacaine is a vasoconstrictor over a wide range of concentrations [15].

In preclinical studies, ropivacaine was shown to have less central nervous and cardiovascular system toxicity than bupivacaine [16–18]. Ropivacaine is less lipid soluble than bupivacaine [19] but has similar protein binding. Its duration of action after extradural administration has been reported as being only slightly less than that of bupivacaine [20] but its shorter systemic half-life should make repeated doses potentially safer [21]. It has greater selectivity for sensory fibres compared with other local anaesthetics and consequently should be associated with less motor block [16, 22]. In addition, inadvertent i.v. injection is likely to produce less cardiac sequelae compared with bupivacaine, but the threshold for convulsions is similar [23].

J. M. EDDLESTON, FRCA, A. CORBETT, FRCA, E. L. HORSMAN, FRCA, Department of Anaesthesia, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL. F. REYNOLDS, MD, FRCA, FRCOG, Department of Anaesthesia, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH. J. J. HOLLAND, FRCA, Department of Anaesthesia, Freeman Hospital, Newcastle upon Tyne. R. P. GRIFFIN, FRCA, Department of Anaesthesia, Guy's Hospital, St Thomas's Street, London SE1 9RT. Accepted for publication: August 3, 1995.

Correspondence to J. M. E.

All of these properties suggest that ropivacaine may be superior to bupivacaine in obstetric analgesia and we have examined this hypothesis in the present study.

Patients and methods

The study was conducted at two centres with similar procedures. Approval was obtained from the hospital Ethics Committees. Written informed consent was obtained from the patients before onset of painful labour. We studied 104 healthy women, aged 18 yr or more, requesting extradural analgesia.

All patients were in established labour and had a singleton healthy pregnancy (36–42 weeks' gestation) with a vertex presentation and a healthy fetal heart rate pattern on cardiotocography. Patients were excluded if the mother had been given more than a single dose of pethidine 125 mg, was greater than 110 kg in weight, less than 150 cm tall, expected fetal weight was < 2.5 kg or the fetus had a suspected abnormality.

Patients were allocated randomly to one of two groups. Group A received bolus doses of 0.25% ropivacaine and group B bolus doses of 0.25% bupivacaine. The drugs were in coded ampoules and the investigators were blinded to the contents. The randomization process was stratified to take into account parity of the patients. Nulliparous parturients received numbers starting from 1 and multiparous parturients from 80 downwards.

An i.v. infusion was established and at least 500 ml of Hartmann's solution was given before extradural block. With the mother in either the sitting or left lateral position, an extradural catheter was inserted in the lumbar region using the loss of resistance technique; 2–3 cm of catheter was left in the extradural space. A test dose of 5 ml of study drug was administered via the extradural catheter. Two minutes later another 5 ml was given. If analgesia was inadequate, the patient received an additional 5 ml of drug extradurally 10 min later.

Subsequently, top-up doses of 10 ml were administered as necessary by the midwife. The minimum time between top-ups was 15 min. The maximum amount of study drug a patient could receive was 95 ml, which corresponded to eight top-up doses. The maximum amount allowed in any 3-h period was 70 ml.

Hypotension was defined as systolic arterial pressure < 90 mm Hg or a reduction in arterial pressure > 30 mm Hg. A hypotensive episode was treated by increasing the rate of the i.v. infusion, positioning the patient on her left side and, if necessary, administering ephedrine. Uterine activity was monitored with an external abdominal transducer and fetal heart rate was recorded using either a scalp electrode or an external ultrasound detector. Oxytocin infusion and Entonox were given as appropriate during the study.

Onset of analgesia was assessed using a pain relief score with each contraction following the initial top-up (1 = no relief; 2 = little relief; 3 = a lot of relief; 4 = complete relief). A score of 3 or 4 was considered satisfactory. Assessment was discontinued when the patient decided analgesia was satisfactory. In addition, a visual analogue pain score (VAS) was recorded before extradural analgesia and then every 15 min until the infant was born.

Assessment of both sensory and motor block was made every 30 min using either ice or ethyl chloride and the Bromage score, respectively. Measurements were continued until return of normal sensation and motor function (Bromage motor score of 0).

The duration of the first and second stages of labour, mode of delivery and birth weight were recorded. In addition, Apgar scores were recorded at 1 and 5 min and umbilical arterial and venous blood samples were obtained at delivery from a clamped section of cord for assessment of $P\text{O}_2$ and pH.

Neurological and adaptive capacity (NAC) scores were recorded at 1.5–2.5 h and 22–26 h after birth. All of these observations were performed by the research fellow in each centre. The NAC score gives a numerical score with a maximum of 40, and an NAC score $\geqslant 35$ is considered to denote a vigorous baby [24].

Patients were withdrawn from the study if analgesia was not satisfactory, the maximum dose of local anaesthetic allowed by the study design was exceeded, the study lasted more than 24 h or delivery was by rotational forceps or Caesarean section.

The mothers and babies were visited daily during their hospital stay and any adverse events were recorded. A general assessment of overall satisfaction with the technique was also recorded. Further follow-up was made by letter or telephone 2–3 weeks after delivery.

STATISTICAL ANALYSIS

Two approaches to the statistical analysis were used: a "per design" analysis and an "all patients treated" analysis. The "per design" (PD) approach was used for analysis of efficacy and the "all patients treated" (APT) approach for analysis of safety.

Data on an interval or ordinal scale were analysed using the stratified Wilcoxon (mid) rank sum test, adjusting for each centre and parity. Analysis of variance was used to check for interaction between strata. P values correspond to two-sided tests and $P < 0.05$ was considered significant. Results are expressed as median (Q1/Q3) unless otherwise stated.

Results

A total of 104 women who requested extradural analgesia for labour were recruited (52 received ropivacaine, 52 bupivacaine). One patient was withdrawn because of technical difficulties (bupivacaine group). Thus we obtained data from 103 patients (ropivacaine 52, bupivacaine 51). Of these 103 women, only 102 received the entire first dose of study drug (one woman (ropivacaine) delivered after the test dose). An additional patient (bupivacaine) delivered before analgesia had occurred after the first dose. Thus 101 patients remained who satisfactorily received analgesia after the full first dose (ropivacaine 51, bupivacaine 50). For statistical analysis, 103

Table 1 Patient characteristics by treatment group (APT group) (mean (SD) [range]). No significant differences between groups

	Ropivacaine ($n = 52$)	Bupivacaine ($n = 51$)
Age (yr)	27.56 [18–42]	26.9 [18–39]
Height (cm)	161.9 (5.8) [150–178]	162.3 (6.5) [150–177]
Weight (kg)	74.4 (9.4) [56–104]	75.7 (10.2) [52–105]
Parity		
Primiparous	31	31
Multiparous	21	20

Table 2 Top-up doses (PD group) required in the two groups (median, Q1, Q3, range). * $P < 0.05$

Group	n	Median	Q1	Q3	Range
Ropivacaine	51	2	1	4	0–8
Bupivacaine	50	3*	1	4	0–7

patients were valid for safety analysis (APT) and 101 for efficacy analysis (PD). Another 17 women (ropivacaine eight, bupivacaine nine) discontinued the study prematurely (appendix). By far the commonest reason for withdrawal was delivery by Caesarean section.

The two groups were well matched in characteristics, parity and number of women who received one dose of pethidine before entering the study (eight ropivacaine, 10 bupivacaine) (table 1). Mean pre-anaesthetic i.v. infusion volumes were similar for each group: ropivacaine ($n = 52$) 653.85 (SD 233.02) (range 500–1000) ml; bupivacaine ($n = 51$) 676.47 (241.32) (500–1000) ml. There was no difference between the groups in the use of Entonox during labour (six ropivacaine, five bupivacaine).

MATERNAL EFFECTS

Top-ups

Eighteen percent of patients in the bupivacaine group required six or more top-ups compared with 7.8% in the ropivacaine group (table 2). The bupivacaine group required significantly more top-ups (3 *vs* 2) ($P < 0.05$) (Wilcoxon rank sum test) to achieve analgesia.

The mean total doses of study drug were: ropivacaine ($n = 52$) 37.69 (median 35.0) (Q1, Q3 25.0, 52.5) (range 5.0–95.0) ml; bupivacaine ($n = 51$) 43.04 (40.0) (25.0, 55.0) (15.0–85.0) ml.

Duration of treatment ranged from 0 to 864 min for the ropivacaine patients ($n = 52$) and from 11 to 710 min for the bupivacaine group ($n = 51$) (ns).

Pain relief

Time to onset of pain relief was 2–59 min (ropivacaine) ($n = 51$) and 1–64 min (bupivacaine) ($n = 50$) with a median onset time of 12 min (ropivacaine) and 10.5 min (bupivacaine) (ns).

Mean individual VAS scores assessed at each contraction after treatment began until the end of the first stage of labour were similar for each group: ropivacaine ($n = 51$) 20.94 (10.00–30.69) (0.61–50.00) mm; bupivacaine ($n = 50$) 15.59 (8.91–26.90) (0.75–62.68) mm. There was no difference between the treatment groups in duration of action of each top-up (table 3).

Table 3 Time between main or additional dose and first top-up dose, and times between supplementary top-ups (PD group) (median Q_1, Q_3, range). No significant differences between groups

Top-up No.		n	Duration of action (min) Median	Q_1	Q_3	Range
1	Ropivacaine	44	62.0	25.5	104.5	18–169
	Bupivacaine	49	56.0	23.0	84.0	12–164
2	Ropivacaine	29	94.0	82.0	119.0	29–249
	Bupivacaine	37	94.0	73.0	121.0	15–244
3	Ropivacaine	23	99.0	79.0	109.0	24–154
	Bupivacaine	28	89.5	66.5	123.0	29–172
4	Ropivacaine	15	94.0	74.0	120.0	23–208
	Bupivacaine	17	76.0	59.0	99.0	29–171
5	Ropivacaine	8	81.0	49.5	131.5	39–169
	Bupivacaine	12	90.0	71.0	124.0	44–174
6	Ropivacaine	4	42.5	14.5	72.0	14–74
	Bupivacaine	9	94.0	69.0	95.0	14–204
7	Ropivacaine	2	41.5	41.0	42.0	41–42
	Bupivacaine	2	82.0	54.0	110.0	54–110
8	Ropivacaine	1	138.0			

Table 4 Distribution of maximum motor block (PD group). No significant differences between groups

Group	Motor block: No motor block	Able to move knee	Able to move foot	Unable to move foot	Total
Ropivacaine	20	17	9	4	50
Bupivacaine	12	19	12	7	50
Total	32	36	21	11	100

Quality of analgesia was assessed the day after delivery in 92 patients and described by most as either excellent or good; 91.1% (ropivacaine), 95.4% (bupivacaine). No patient described pain relief as poor.

Upper segmental level of analgesia was assessed in 101 patients. The median level was T8 for both groups (range T3–T11 for ropivacaine ($n = 51$) and T2–T11 for bupivacaine ($n = 50$)). Motor block was assessed in 100 patients. The treatment groups did not differ in maximum motor block during the study period (table 4). However, 20 patients in the ropivacaine group failed to experience any motor weakness compared with 12 in the bupivacaine group (ns). The median duration for those with block was shorter in the ropivacaine ($n = 28$) 100.5 (Q1, Q3 65.5–180.0) min compared with the bupivacaine ($n = 32$) 161.0 (120.0–206.0) min group.

There was no difference between the groups in duration of the stages of labour (first stage: ropivacaine ($n = 45$) 257.0 (112.0–357.0) min, bupivacaine ($n = 44$) 231.5 (157.5–400.0) min; second stage: ropivacaine ($n = 45$) 55.0 (32.0–98.0) min, bupivacaine ($n = 44$) 66.5 (31.5–107.0) min). Patients who were delivered by Caesarean section were excluded from the analysis.

Table 5 Apgar score at 1 and 5 min, umbilical cord pH and Po_2 (kPa) at delivery (APT group) and neuroadaptive capacity (NAC) score at 2 (0.5) and 24 (2) h after delivery (PD group) (median, Q_1, Q_3, range). n = Number of babies. No significant differences between groups

	n	Ropivacaine	n	Bupivacaine
Apgar				
1	48	8.5 (7, 9) (5–10)	49	8.0 (7, 9) (1–10)
5	49	10.0 (9, 10) (8–10)	49	10.0 (9, 10) (4–10)
Umbilical vein				
pH	44	7.34 (7.29, 7.39) (7.06–7.46)	43	7.34 (7.30, 7.38) (7.19–7.48)
Po_2	32	25.00 (20, 29.55) (2.56–37.10)	29	24.30 (20.50, 29.80) (13.20–35.40)
Umbilical artery				
pH	43	7.25 (7.2, 7.32) (7.0–7.37)	41	7.25 (7.20, 7.30) (7.09–7.37)
Po_2	32	15.20 (10.9, 19.15) (6.00–32.90)	28	13.45 (10.35, 16.90) (3.30–27.90)
NAC score				
2 h	43	36 (35, 38) (32–39)	42	36 (36, 37) (29–40)
24 h	43	38 (37, 39) (33–40)	40	37 (36, 38) (30–39)

Women who received ropivacaine had an incidence of unassisted vaginal delivery (36 women) of 70.59 % compared with 52.0 % for the bupivacaine group (26 women) (ns). The number delivered by non-rotational low forceps in the bupivacaine group was 12 (24.00 %) compared with six (11.77 %) in the ropivacaine group (ns).

The remaining babies were delivered either by Caesarean section (five (9.8 %) ropivacaine, six (12 %) bupivacaine); vacuum extraction (three (5.9 %) ropivacaine; five (10.0 %) bupivacaine); or mid or high forceps (one (1.96 %) ropivacaine; one (2.00 %) bupivacaine (ns)).

FETAL EFFECTS

Birth weights for the groups were similar: ropivacaine ($n = 52$) 3410 g (Q1, Q3 3110, 3665 g) (range 2560–4650 g); bupivacaine ($n = 49$) 3400 g (3160, 3900 g) (2360–4470 g).

There was no difference between the groups in the condition of the neonate at delivery or at 24 h, as assessed by Apgar score, umbilical cord acid–base status and NAC scores, respectively (table 5).

Adverse events were classified as mild, moderate or severe. There were 66 maternal events (ropivacaine 37; bupivacaine 29). The majority (42) were mild (ropivacaine 23, bupivacaine 19). Mild events ranged from paraesthesia with extradural catheter insertion, cardiovascular alteration, poor/failed progression of labour, Caesarean section, postnatal depression and postpartum infective episodes such as cystitis or upper respiratory tract infection. The commonest single events were paraesthesia (seven cases) with insertion of the extradural catheter, and backache after delivery (seven cases). All patients either recovered spontaneously or had improved by the 2–3-week follow-up. Those women who delivered ultimately by Caesarean section (10) were classified as adverse events (nine maternal, one fetal).

Moderate events again included poor or failed progression of labour. In addition, events such as retrosternal pain, diarrhoea, tachycardia, nausea and vomiting, and vaginal and uterine haemorrhage were classified as moderate. One event was described as severe (uterine haemorrhage in the bupivacaine group). The patient had no long-term sequelae.

In the fetuses, 60 events were reported (31 ropivacaine, 29 bupivacaine): 50 % were described as mild (16 ropivacaine, 14 bupivacaine). With the exception of one patient (bupivacaine), these were cases of fetal bradycardia. Another 19 episodes of bradycardia were reported (12 moderate, seven severe).

Sixteen adverse events were described in the neonates (six ropivacaine, 10 bupivacaine). Similarly, the majority were mild (three ropivacaine, nine bupivacaine). The commonest event reported was jaundice (seven cases). All neonates recovered spontaneously.

Discussion

Ropivacaine should possess lower systemic toxicity than bupivacaine. In practice, although there is disparity between animal species in absolute cardiac and central nervous system toxicity [16, 17], Scott and colleagues [23] predicted less cardiovascular toxicity with ropivacaine than with bupivacaine in human volunteers after i.v. administration. This was deduced from analysis of the electrocardiograph.

To date, ropivacaine has been administered in clinical practice by several routes and over a range of concentrations (0.1–1 %). It has been shown to provide comparable analgesia–anaesthesia by the extradural route as bupivacaine for a variety of surgical procedures [20, 25], but uncertainty still exists over the relative depth of motor block with the two agents.

Our study suggested that 0.25 % ropivacaine and bupivacaine produced comparable analgesia in labour, in terms of onset, maximum level of sensory block and degree of patient satisfaction. Interestingly, bupivacaine-treated patients required more supplementary top-up doses to maintain effective analgesia.

Although there was no statistically significant difference in degree of motor block (as assessed by the Bromage score), there was a higher proportion of patients with no motor block in the ropivacaine-treated group. Similarly, and possibly linked, was the finding that a greater number of women in this group had spontaneous vaginal delivery. Unfortunately, one criticism of the Bromage score is that it incorporates an assessment of degree of spread of local anaesthetic in addition to depth of motor block. A more sensitive assessment of motor function would be isometric testing. This could be performed by assessment of the abdominal wall by a quantified electromyographic method and in the lower extremities by mechano-transducers [26].

Assessment of the effect of a local anaesthetic on the fetus is always difficult and relies largely on evaluation of the infant at delivery and over the ensuing hours. Traditionally, neonatal condition has been assessed with the Apgar scoring system and umbilical cord acid–base status.

To distinguish the effects of a drug on a neonate from those caused by *in utero* asphyxia requires more detailed assessment. Amiel Tison and colleagues developed the NAC score for this purpose [24]. It has been shown clinically to be a valid and sensitive test for evaluating neurobehavioural performance scores when comparing general with regional anaesthesia for Caesarean section [27]. Our study failed to demonstrate any difference between the groups in NAC scores or in the acid–base status of the infant at delivery.

We conclude that 0.25 % ropivacaine and 0.25 % bupivacaine produced comparable and effective maternal pain relief in labour without detriment to the fetus.

Acknowledgements

This study was supported by Astra Pain Control AB Sodertalje, Sweden. We thank Ms Cecilia Hedlund, Department of Biostatistics, Astra Pain Control, Sweden.

References

1. Robinson JD, Rosen M, Evans JM, Revill SI, David H, Rees GAD. Maternal opinion about analgesia for labour. A controlled trial between epidural block and intramuscular pethidine combined with inhalation. *Anaesthesia* 1980; **35**: 1173–1181.
2. Studd JWW, Crawford JS, Duigan NN, Rowbotham CJF, Hughes AD. The effect of lumbar epidural analgesia on the rate of cervical dilatation and the outcome of labour of spontaneous onset. *British Journal of Obstetrics and Gynaecology* 1980; **87**: 1015–1021.
3. MacArthur C, Lewis M, Know EG, Crawford JS. Epidural anaesthesia and longterm backache after childbirth. *British Medical Journal* 1990; **301**: 9–12.
4. Albright G. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979; **51**: 285–287.
5. Reiz S, Nath S. Cardiotoxicity of local anaesthetic agents. *British Journal of Anaesthesia* 1986; **58**: 736–746.
6. Reynolds F. Ropivacaine. *Anaesthesia* 1991; **46**: 339–340.
7. Abboud TK, Khoo SS, Miller F, Doan T, Herriksen EH. Maternal, fetal and neonatal responses after epidural anesthesia with bupivacaine, 2-chloroprocaine or lidocaine. *Anesthesia and Analgesia* 1982; **61**: 638–644.
8. Scanlon JW, Brown WH, Weiss JB, Alpar MH. Neurobehavioral responses of newborn infants after maternal epidural anesthesia. *Anesthesiology* 1974; **40**: 121–128.
9. Abboud TK, Afrusiabi A, Sarkis F, Kuhner B, Daltarian F, Nagappala S, Miller F. Continuous infusion epidural analgesia in parturients receiving bupivacaine, chloroprocaine, or lidocaine—maternal, fetal and neonatal effects. *Anesthesia and Analgesia* 1984; **63**: 421–428.
10. Kuhnert BR, Harrison MJ, Linn PL, Kuhnet PM. Effects of maternal epidural anesthesia on neonatal behavior. *Anesthesia and Analgesia* 1984; **63**: 301–308.
11. Eddleston JM, Maresh M, Horsman EL, Young H, Lacey P, Anderton J. Comparison of the maternal and fetal effects associated with intermittent or continuous infusion of extradural analgesia. *British Journal of Anaesthesia* 1992; **69**: 154–158.
12. Jones G, Paul OL, Elton RA, McClure JH. Comparison of bupivacaine and bupivacaine with fentanyl in continuous extradural analgesia during labour. *British Journal of Anaesthesia* 1989; **63**: 254–259.
13. Murphy JD, Henderson K, Bowden MI, Lewis M, Cooper GM. Bupivacaine versus bupivacaine plus fentanyl for epidural analgesia: effect on maternal satisfaction. *British Medical Journal* 1991; **302**: 564–567.
14. Yan G, Gregory MA, Gin T, Oh TE. Obstetric epidural analgesia with mixtures of bupivacaine, adrenaline and fentanyl. *Anaesthesia* 1990; **45**: 1020–1023.
15. Kopacz DJ, Carpenter RL, Mackey DC. Effect of ropivacaine on cutaneous capillary blood flow in pigs. *Anesthesiology* 1989; **71**: 69–74.
16. Reiz S, Haggmark S, Johannson G, Nath S. Cardiotoxicity of ropivacaine: A new amide local anaesthetic agent. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 93–98.
17. Feldman HS, Arthur GR, Covino BG. Comparative systemic toxicity of convulsant and supraconvulsant doses of intravenous ropivacaine, bupivacaine and lidocaine in the conscious dog. *Anesthesia and Analgesia* 1989; **69**: 794–801.
18. Feldman HS, Arthur GR, Pitkanen M, Hurley R, Doucette AM, Covino BG. Treatment of acute system toxicity after the rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. *Anesthesia and Analgesia* 1991; **73**: 373–384.
19. Rosenberg PH, Kytha J, Alila A. Absorption of bupivacaine, etidocaine, lignocaine and ropivacaine into N-heptane rat sciatic nerve and human extradural and subcutaneous fat. *British Journal of Anaesthesia* 1986; **58**: 310–314.
20. Brown DL, Carpenter RL, Thompson GE. Comparison of 0.5 % ropivacaine and 0.5 % bupivacaine for epidural anesthesia in patients undergoing lower extremity surgery. *Anesthesiology* 1990; **72**: 633–636.
21. Lee A, Fagan D, Lamont M, Tucker GT, Halldian M, Scott DB. Disposition kinetics of ropivacaine in humans. *Anesthesia and Analgesia* 1989; **69**: 736–738.
22. Feldman HS, Covins, BG. Comparative motor blocking effects of bupivacaine and ropivacaine, a new aminoamide local anesthetic in the rat and dog. *Anesthesia and Analgesia* 1988; **67**: 1047–1052.
23. Scott DB, Lee A, Fagan D, Bowler GMR, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesthesia and Analgesia* 1989; **69**: 563–569.
24. Amiel Tison C, Barrier G, Shnider SM, Levinson G, Hughes SC, Stephani SJ. A new neurologic and adaptive capacity scoring system for evaluating obstetric medications in full-term newborns. *Anesthesiology* 1982; **56**: 340–350.
25. Morrison LMM, Emanuelsson BM, McClure JH, Pollok AJ, McKeown DW, Brockway M, Jozwiak H, Wildsmith JAW. Efficacy and kinetics of extradural ropivacaine: comparison with bupivacaine. *British Journal of Anaesthesia* 1994; **72**: 164–169.
26. Zaric D, Axelsson K, Nydahl PA, Philipson L, Samuelsson L. Sensory and motor blockade during continuous epidural infusion of ropivacaine 0.1 %, 0.2 %, 0.3 % in volunteers—a double blind study. *Regional Anesthesia* 1994; **19** (Suppl. 2S): 60.
27. Abboud TK, Nagappala S, Murakawa K, Davis S, Haroutunian S, Zakarian M. Comparison of the effects of general and regional anesthesia for Cesarean section on neonatal neurologic and adaptive capacity scores. *Anesthesia and Analgesia* 1985; **64**: 996–1000.

Appendix

LIST OF PATIENTS AND REASON FOR DISCONTINUATION
(*Manchester, †London). LSCS = Lower segment Caesarean section

Reason	Group	Patient No.
1. Adverse event	Ropivacaine	5† Second set of NACS not performed
		13† Fetal distress → LSCS
	Bupivacaine	33* Fetal distress → LSCS
2. Other	Ropivacaine	5* Failure to progress → LSCS
		8* Extradural topped up with bupivacaine
		35* Brow presentation → LSCS
		4† Bupivacaine given
		8† Fetal distress → LSCS
		80† LSCS
	Bupivacaine	3* Delivered before analgesia
		17* Failure to progress → LSCS
		57* Extradural catheter displaced
		62* Failure to progress → LSCS
		11† LSCS
		14† Prepared for LSCS—finally delivered by forceps
		15† Patient request
		70† Failure to progress → LSCS
Deviation from protocol	Ropivacaine	79† Rapid delivery
	Bupivacaine	44* Baby underweight
		48* Baby underweight

British Journal of Anaesthesia 1996; **76**: 72–76

Absence of an early pre-emptive effect after thoracic extradural bupivacaine in thoracic surgery

J. L. AGUILAR, R. RINCÓN, V. DOMINGO, P. ESPACHS, M. J. PRECIADO AND F. VIDAL

Summary

We have determined if thoracic extradural block before surgical incision for thoracotomy produces pre-emptive analgesia. Using a double-blind, placebo-controlled, crossover design, 45 patients (ASA II–III) undergoing posterolateral thoracotomy for lung resection were randomized to one of three groups: group 1 received 0.5% bupivacaine and adrenaline 1/200000 (B+E) 8 ml through a thoracic extradural catheter (tip T3–T5) 30 min before skin incision and saline 8 ml 15 min after skin incision; group 2 received saline 8 ml extradurally before incision and B+E 8 ml after incision; group 3 received saline 8 ml extradurally before and after incision. General anaesthesia was induced and maintained with propofol, alfentanil and atracurium. The alfentanil infusion was stopped before chest closure and fentanyl 50 μg in saline 10 ml was given extradurally. Patient-controlled extradural analgesia (PCEA) was commenced with 0.125% bupivacaine, adrenaline 1/400000 and fentanyl 6 μg ml^{-1} (continuous rate of 2 ml h^{-1} and supplementary doses of 0.5 ml per 6 min). Visual analogue scale (VAS) scores (recorded at rest, on mobilization and after cough), verbal rating scale (VRS) (recorded at rest), number of successful PCEA demands and complications were measured during the first 48 h after operation. There was no significant difference between groups, either in PCEA requirements ($P > 0.21$) or in VAS scores (either at rest, during mobilization of the ipsilateral arm of surgery or after cough). No significant differences between groups were found in the VRS. Thoracic extradural block with bupivacaine did not produce an early preemptive effect after thoracotomy. (*Br. J. Anaesth.* 1996; **76**: 72–76)

Key words

Analgesia, pre-emptive. Pain, postoperative. Surgery, thoracic. Analgesic techniques, extradural. Anaesthetics local, bupivacaine.

In animals, tissue injury or brief afferent C-fibre conditioning stimuli results in increased excitability and expansion of the cutaneous receptive fields of flexor motor neurones and dorsal horn neurones [1, 2]. Central neurones may alter their structure or function as a result of past experience or injury [3]. Recordings from the spinal cord show that conduction between neurones is altered during noxious stimulation and may induce a hyperexcitable state, a phenomenon termed "wind-up" that may relate to a "pain memory", so that further stimuli are then said to potentiate the neural impulses and intensify the pain [4]. These experiments gave support to the concept of "pre-emptive analgesia."

However, the results of clinical studies are debatable. Conventional doses of oral NSAID appear to have no additional clinical benefit when given before compared with after surgery [5, 6]. Pre-emptive field block studies with local anaesthetics are inconclusive [7, 8]. I.v. opioids may confer some advantage when given pre-emptively [9]. Some studies on pre-emptive extradural block support the hypothesis, either with local anaesthetics [10] or opioids alone [11], using in both cases a lumbar approach. When opioids and local anaesthetics were combined, no pre-emptive effect was shown [12].

The aim of this study was to determine if extradural thoracic block with local anaesthetic before surgical incision had a pre-emptive effect on postoperative pain intensity in patients undergoing thoracotomy.

Patients and methods

The study was approved by the Institutional Review Board (IRB) and written informed consent was obtained from all patients. Forty-five patients, ASA II–III, undergoing posterolateral thoracotomy for lung resection were allocated randomly to one of three groups and studied prospectively in a double-blind, placebo-controlled, crossover design.

All patients were familiarized with the following pain intensity measurements: 10-cm linear visual analogue scale (VAS); verbal rating scale (VRS) described as: no pain, slight, moderate, strong, intense and unbearable; and patient-controlled extradural analgesia (PCEA) pump management.

Preoperative investigations in all patients included arterial blood-gas measurements, pulmonary function tests, haematology, coagulation, biochemical

---

J. L. AGUILAR, MD, PHD, DEAA, R. RINCÓN, MD, V. DOMINGO, MD, P. ESPACHS, MD, M. J. PRECIADO, MD, DEAA, F. VIDAL, MD, Department of Anaesthesiology, Hospital Universitario Germans Trias i Pujol, Badalona, Barcelona, Spain. Accepted for publication: September 5, 1995.

screening and thoracic radiology. Exclusion criteria were: renal disease (creatinine > 106 μmol litre^{-1}), hepatic disease (bilirubin > 20 μmol litre^{-1}), congestive heart failure, atrioventricular heart block, epilepsy, alcoholism, hypovolaemia, age less than 18 or more than 76 yr, metrizamide allergy, a history of chronic pain or regular intake of analgesic drugs, a psychiatric history, any contraindication to regional anaesthesia and failure to comprehend PCEA or any of the pain intensity scales.

A table of random numbers was used to generate a randomization schedule to which each patient would be assigned upon entry into the trial. An envelope containing the group assignment (and the order of bupivacaine and saline infusions) was prepared, sealed and numbered for each patient. On the morning of surgery, one of the investigators opened the envelope and prepared two identical syringes that were labelled for pre-incisional and post-incisional infusions. This investigator had no further involvement with the study. All patients and personnel involved in patient management and data collection were unaware of the group to which the patient had been allocated. Although the anaesthetist in charge of the case also was unaware of the patient's group, he had ready access to this information in the event of an emergency.

The day before surgery, an extradural thoracic catheter was inserted and its tip placed at T3–5 using an 18-gauge Tuohy needle [13]. The position of the catheter tip was checked using an image intensifier by administration of metrizamide.

Two different extradural solutions were used: 0.5 % bupivacaine with adrenaline 5 μg ml^{-1} (B) and saline solution (S), in a total volume of 8 ml for each dose. The first extradural dose was administered 30 min before surgical incision and the second 15 min after.

Lorazepam 1 mg was administered orally on the night before surgery and 1 h before anaesthesia. Ringer's lactate solution 1 litre was administered i.v. and a radial artery cannula inserted. EEG, non-invasive arterial pressure, Sp_{O_2} and expired carbon dioxide were monitored. Anaesthesia was induced with propofol 2 mg kg^{-1}, alfentanil 15 μg kg^{-1} and atracurium 0.5 mg kg^{-1} to facilitate tracheal intubation with a double-lumen tracheal tube. Anaesthesia was maintained with a continuous infusion of propofol 6 mg kg^{-1} h^{-1}, alfentanil 1 μg kg^{-1} min^{-1} and atracurium 0.3 mg kg^{-1} h^{-1}. Alfentanil 5 μg kg^{-1} was given every 5 min if arterial pressure or heart rate was 25 % or more than baseline. The lungs were ventilated with 100 % oxygen. The alfentanil infusion was stopped before chest closure. At the end of operation residual neuromuscular block was antagonized with neostigmine, and atropine and fentanyl 50 μg in 10 ml of saline solution were given extradurally. The trachea was extubated immediately after surgery and the patient transferred to the recovery room.

In the recovery room, an extradural infusion of 0.125 % bupivacaine with adrenaline 1/400000 and fentanyl 6 μg ml^{-1} was started using a PCEA pump system (Pharmacia Deltec). A continuous rate of 2 ml h^{-1} and supplementary boluses of 0.5 ml, with a 6-min lockout interval, were given during the first 48 h after operation. PCEA was then stopped and restarted if analgesia was inadequate. The following analgesic regimen was then commenced: tramadol 1 mg kg^{-1} i.v. every 6 h alternated with metamizol 30 mg kg^{-1} i.v. every 6 h for 3 days. When i.v. medication was impractical, the same analgesic regimen was maintained by the oral route, with consequent reduction in dosage. The thoracic extradural catheter was removed when oral administration began.

Pain scores at rest, during abduction of the ipsilateral arm and after cough were recorded on a 10-cm linear VAS at 1, 3, 7, 11, 19 and 43 h after surgery. Pain scores at rest were also determined at the same times on a VRS. Total successful PCEA demands were recorded at 18 and 48 h after operation. Arterial blood-gas analysis was performed at 1, 3, 7, 19 and 43 h after operation. Side effects (nausea, vomiting, pruritus, respiratory depression and hypotension) were recorded.

DATA ANALYSIS

We estimated the sample size required for a test assuming that postoperative pain would be less intense in group 1 (extradural bupivacaine before surgical incision) than in the two other groups. Using as a principal variable the VAS for postoperative pain and considering a difference of ±2 cm as clinically significant, we calculated the sample size required. Considering a type I α error of 0.05 and a type II β error of 0.1, assuming a minimized, although not fully absent, type II β error, the sample size was calculated as 15 patients in each group.

Eight patients were withdrawn from the study because of: inadequate pain relief in spite of PCEA as a result of ipsilateral shoulder pain ($n = 5$; two in group 1, two in group 2 and one in group 3); loss of the extradural catheter before the end of the study ($n = 1$; group 2); or incomplete data collection ($n = 2$; one in group 1 and one in group 2). The patients withdrawn were replaced until 45 patients had completed the study.

Qualitative data (sex, type of intervention and verbal categoric scale) were assessed by a chi-square test with Yates' correction, when necessary. Quantitative data were examined with analysis of variance according to Scheffé's procedure. Differences between groups were tested with the two-tailed Student's test. The Kruskall–Wallis test was used for non-parametric data. Values of $P < 0.05$ were considered significant.

Results

There were no significant differences between groups in age, weight, height, sex, type of surgical procedure or duration of surgery (table 1).

The total doses of alfentanil, propofol and atracurium, and the bolus of alfentanil received in the intraoperative period by each patient did not differ significantly between the groups (table 1).

There were no differences in VAS scores either at

Table 1 Patient data and clinical variables (mean (SD) [SEM or range])

Variable	Group 1	Group 2	Group 3
Age (yr)	60.5 (11) [37–77]	58.8 (11.8) [31–72]	57 (0.7) [30–71]
Weight (kg)	70 (10.7) [2.7]	70 (14.2) [3.6]	65 (9.7) [2.5]
Height (cm)	162 (7.8) [2]	161 (6.6) [1.7]	166 (7) [1.8]
Duration of surgery (min)	154 (60.7) [15.7]	127 (47.6) [12.3]	142 (54.1) [13.9]
Sex (M/F) (%)	87/13	80/20	73/27
Surgical procedures (%)			
Pneumectomy	13	27	20
Lobectomy	67	53	40
Miscellaneous	20	20	40
Propofol (mg)	1369 (508) [131]	1094 (419) [108]	1179 (427) [110]
Atracurium (mg)	108 (29) [7.5]	90 (21) [5.4]	91 (22) [5.7]
Alfentanil (mg)	12.5 (4.9) [1.2]	10.0 (3.0) [0.7]	10.8 (4.1) [1]
Bolus alfentanil	0.8 (0.9) [0.2]	1.0 (1.6) [0.4]	2.4 (2.2) [0.6]

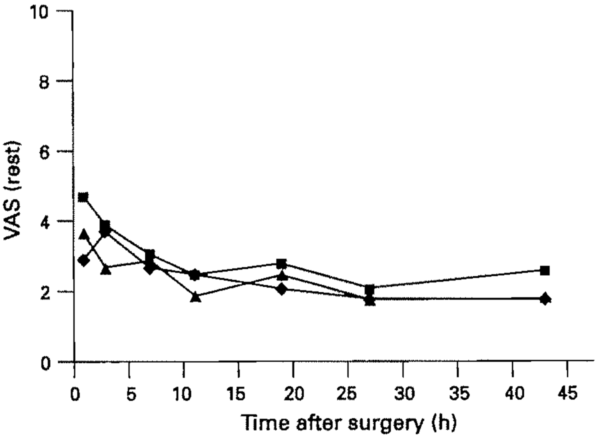


Figure 1 VAS pain intensity at rest throughout the study in the bupivacaine–saline (■), saline–bupivacaine (▲) and saline–saline (◆) groups.

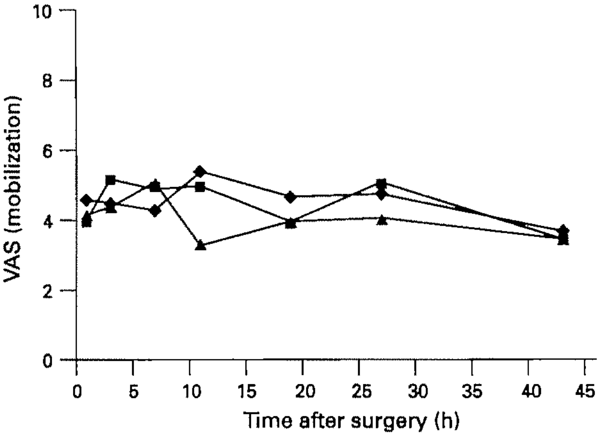


Figure 2 VAS pain intensity after abduction of the ipsilateral arm throughout the study in the bupivacaine–saline (■), saline–bupivacaine (▲) and saline–saline (◆) groups.

rest (fig. 1), during mobilization of the ipsilateral arm of surgery (fig. 2) or after cough (fig. 3). There were no significant differences between groups in VRS (table 2) or in requirements for PCEA (table 3).

Arterial blood-gas analyses showed no significant differences (table 4) between groups.

No complications or adverse effects were observed in any of the patients.

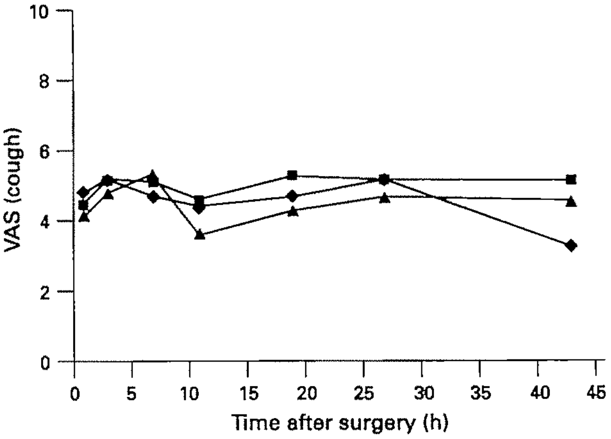


Figure 3 VAS pain intensity after coughing throughout the study in the bupivacaine–saline (■), saline–bupivacaine (▲) and saline–saline (◆) groups.

Discussion

We found no significant differences in pain scores at rest, during mobilization of the ipsilateral arm or after cough between patients with pre-incisional (30 min) and post-incisional (15 min) administration of a thoracic extradural with 0.5% bupivacaine using the suggested design for studies of pre-emptive analgesia [14]. There may be several explanations for the difference between our findings and those of previous studies. Although central sensitization may contribute to postoperative pain in humans, surgical trauma differs from the conditioning stimuli applied in experimental studies in several aspects. Contrary to a well-localized thermal or chemical injury, or brief C-afferent stimulation, the afferent input to the CNS during surgery is extensive, with mixed cutaneous, muscular and visceral components. In thoracic surgery there are several noxious peri-operative events, such as rib retractor placement, insertion of chest drains, intercostal nerve damage, rib fractures and stripping of the periosteum. Surgery may be considered as an uncontrolled prolonged stimulus involving generation of afferent stimuli from somatic and visceral fibres and may not, therefore, be directly comparable with experimental models. Moreover, this afferent input is maintained while the inflammatory surgical response lasts.

Our findings contrast with those of Katz and

Table 2 Verbal rating scale (number of patients)

	Group 1					Group 2					Group 3				
	1 h	3 h	11 h	27 h	43 h	1 h	3 h	11 h	27 h	43 h	1 h	3 h	11 h	27 h	43 h
No pain	5	—	1	1	—	3	1	1	3	1	1	1	2	3	2
Slight	2	6	7	10	10	5	5	4	7	7	2	3	6	5	4
Moderate	2	4	5	2	5	2	6	7	4	6	9	8	6	6	8
Strong	1	1	1	1	—	2	2	1	1	1	1	1	1	—	1
Intense	1	3	—	—	—	1	1	—	—	—	—	1	—	—	—
Unbearable	2	1	—	—	—	—	—	—	—	—	1	1	—	—	—

Table 3 PCEA boluses in the three groups (mean (SD) [SEM])

PCEA	Group 1	Group 2	Group 3	P
18 h	58.8 (37.8) [9.7]	42.6 (31.5) [8.1]	53.8 (28.5) [7.3]	0.441
48 h	127.4 (65.9) [17.6]	102.8 (49.2) [12.7]	95.8 (57.4) [14.8]	0.506

Table 4 Arterial blood-gas analyses (mean (SD))

	Group 1			Group 2			Group 3		
	7 h	19 h	43 h	7 h	19 h	43 h	7 h	19 h	43 h
pH	7.3 (0.02)	7.3 (0.03)	7.4 (0.02)	7.3 (0.02)	7.4 (0.02)	7.4 (0.03)	7.3 (0.02)	7.4 (0.01)	7.4 (0.02)
P_{O_2} (kPa)	9.36 (1.36)	9.41 (1.53)	7.89 (1.85)	10.33 (3.05)	9.80 (2)	7.84 (1.82)	9.39 (1.94)	9.49 (1.92)	7.65 (1.34)
P_{CO_2} (kPa)	5.61 (0.53)	5.64 (0.6)	5.32 (0.68)	5.44 (0.61)	5.5 (0.53)	5.38 (0.66)	5.31 (0.48)	5.28 (0.37)	5.64 (0.57)

colleagues [11], although we used similar administration times. They used the lumbar extradural route and gave fentanyl 4 µg kg^{-1}. We used the thoracic approach and gave 0.5 % bupivacaine 8 ml.

Our negative results could be caused by administration of too small a dose of extradural bupivacaine which may not be sufficient to provide good afferent block [15]. Furthermore, the block was instituted 30 min before surgery which might not be long enough for optimal pre-emptive analgesia, although a clinically effective block would have been achieved.

Katz and colleagues used i.v. PCA with morphine while we used PCEA. They found a significantly increased analgesic effect only at 6 h and reduced morphine consumption between 12 and 24 h after surgery in the treated group [11] (pain scores and postoperative morphine consumption were reduced only at one of five assessments). Total morphine consumption however was almost identical in both groups. The pre-emptive study group was older and included more females than the control group, both of which factors may result in less pain and opioid consumption [16].

An explanation for our failure to show a pre-emptive effect could be that central sensitization was induced equally in the three groups, as a result of insufficient afferent block. Conventional extradural block may not provide total C-afferent block and the vagi and phrenic nerves are unaffected [17]. Extradural block in our study was obtained with a potent local anaesthetic (bupivacaine 5 mg ml^{-1} (8 ml)) suitable for surgical anaesthesia, but the degree of afferent block was not established with any objective method.

Pre-emptive, balanced (combining NSAID, opioids, local anaesthetics and other drugs) and prolonged analgesia throughout the inflammatory response has been suggested as the only way to induce a significant effect on pain intensity. A single extradural dose cannot be expected to have prolonged effects; a secondary neuroplastic response may be expected when the block wears off [18].

C-afferent activity may be generated not only during surgery, but also in the postoperative period, partly as a result of persistent inflammation and hyperalgesia at the wound site. This activity may be sufficient to produce central sensitization and no information is available on the optimal duration of afferent block to prevent alterations in dorsal horn neurones. In our design, central sensitization may have occurred in the pre-emptive study group (group 1) during the postoperative period when the concentration of bupivacaine used for continuous extradural infusion was small. It may be that the windup process outlasts the effect of bupivacaine. What we thought was pre-emptive analgesia may merely have been pre-incisional. The prevention of pain must begin before operation and then continue during and after operation [19].

It has been suggested that administration of opioids as premedication or during induction and maintenance of anaesthesia may attenuate central hyperactivity and consequently confound postoperative assessments of pain and analgesic requirements [9, 11, 20]. Morphine has been shown to prevent the establishment of central sensitization [21] in rats. In a recent study [9], morphine 10 mg i.v. was more effective when administered before compared with after hysterectomy. In our study, however, it is remarkable that although the number of doses of alfentanil given during the intraoperative period was greater in group 3 (S-S), there were no significant differences in postoperative pain assessments between groups. Clinical studies of pre- *vs* postoperative opioids [9, 11] seem to confirm the theoretical importance of pre-emptive analgesia [22], but only very minor and shortlasting advantageous effects have been documented.

The potential pre-emptive effect of an extradural test dose with local anaesthetic is also controversial. One study found no significant differences in pain and opioid requirements after identical pre- or postoperative extradural block with bupivacaine in patients undergoing abdominal hysterectomy [23], while a recent study [10] during lower abdominal surgery showed a reduction in the required dose of morphine and McGill pain questionnaire, although VAS did not differ significantly. In an earlier study, patients undergoing colonic surgery given either an extradural dose of bupivacaine 7 ml (7.5 mg $\mathrm{ml^{-1}}$) with morphine 2 mg before or after surgery, followed by continuous extradural bupivacaine 0.25 mg $\mathrm{ml^{-1}}$ (4 ml $\mathrm{h^{-1}}$ for 72 h) showed no significant differences in pain scores at rest or during mobilization, or in requests for additional morphine [12].

It may be suggested that wound hyperalgesia is a more sensitive measure of pain reduction. Hyperalgesia (increased sensitivity and extended sensory fields) may be the earliest and most sensitive manifestation of inadequate antinociceptive control and could be investigated in future studies by measuring sensory and pain cutaneous thresholds. However, the clinical relevance of these measures is not great. A recent study of fentanyl or ketamine i.v. [24] found no statistically significant changes in spontaneous incisional or movement-associated pain compared with the control group, although the intensity of pain to suprathreshold pressure on the wound was decreased in both treatment groups compared with the control group.

Acknowledgements

We thank Dr H. Kehlet for his help and advice. Supported in part by a grant from Fondo de Investigaciones Sanitarias (FIS 94/0642), Spanish Health Ministry.

References

1. Hylden JLK, Nahin RL, Traub RJ, Dubner R. Expansion of receptive fields of spinal lamina I projection neurons in rats with unilateral adjuvant-induced inflammation: the contribution of dorsal horn mechanisms. *Pain* 1989; **37**: 229–243.
2. Coderre TJ, Vaccarino AL, Melzack R. Central nervous system plasticity in the tonic pain response to subcutaneous formalin injection. *Brain Research Reviews* 1990; **535**: 155–158.
3. Woolf CJ. Recent advances in the pathophysiology of acute pain. *British Journal of Anaesthesia* 1989; **63**: 139–146.
4. Wall PD. The prevention of postoperative pain. *Pain* 1988; **33**: 289–290.
5. Hill CM, Carroll MJ, Giles AD, Pickvance N. Ibuprofen given pre and postoperatively for the relief of pain. *International Journal of Oral and Maxillofacial Surgery* 1987; **16**: 420–424.
6. Sisk AL, Graver BJ. A comparison of preoperative and postoperative naproxen sodium for suppression of postoperative pain. *International Journal of Oral and Maxillofacial Surgery* 1990; **48**: 674–678.
7. Dierking GW, Dahl JB, Kanstrup J, Dahl A, Kehlet H. Effect of pre- *vs* postoperative inguinal field block on postoperative pain after herniorrhaphy. *British Journal of Anaesthesia* 1992; **68**: 344–348.
8. Ejlersen E, Andersen HB, Eliasen K, Mogensen T. A comparison between preincisional and postincisional lidocaine infiltration and postoperative pain. *Anesthesia and Analgesia* 1992; **74**: 495–498.
9. Richmond CE, Bromley LM, Woolf CJ. Preoperative morphine pre-empts postoperative pain. *Lancet* 1993; **342**: 73–75.
10. Katz J, Clairoux M, Kavanagh BP, Roger S, Nierenberg H, Redahan C, Sandler AN. Pre-emptive lumbar epidural anaesthesia reduces postoperative pain and patient-controlled morphine consumption after lower abdominal surgery. *Pain* 1994; **59**: 395–403.
11. Katz J, Kavanagh BP, Sandler AN, Nierenberg H, Boyland JF, Friedlander M, Shaw BF. Preemptive analgesia. Clinical evidence of neuroplasticity contributing to postoperative pain. *Anesthesiology* 1992; **77**: 439–446.
12. Dahl JB, Hansen BL, Hjortso NC, Erichsen CJ, Moiniche S, Kehlet H. Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery. *British Journal of Anaesthesia* 1992; **69**: 4–8.
13. Simpson BR, Parkhouse J, Marshall R, Lambrechts W. Extradural analgesia and the prevention of postoperative respiratory complications. *British Journal of Anaesthesia* 1961; **33**: 628–641.
14. McQuay HJ, Dickenson AH. Implications of nervous system plasticity for pain management. *Anaesthesia* 1990; **45**: 101–102.
15. Lund C, Selmar P, Hansen OH, Hjortso NC, Kehlet H. Effects of epidural bupivacaine on somatosensory evoked potentials after dermatomal stimulation. *Anesthesia* and *Analgesia* 1987; **66**: 34–38.
16. Dahl JB, Kehlet H. The value of pre-emptive analgesia in the treatment of postoperative pain. *British Journal of Anaesthesia* 1993; **70**: 434–439.
17. Dahl JB, Rosenberg J, Lund C, Kehlet H. Effect of thoracic epidural bupivacaine 0.75% on somatosensory evoked potentials after dermatomal stimulation. *Regional Anesthesia* 1990; **15**: 73–75.
18. Breivik H. Pre-emptive analgesia. *Current Opinion in Anesthesiology* 1994; **7**: 458–461.
19. Moote C. Techniques for post-op pain management in the adult. *Canadian Journal of Anaesthesia* 1993; **40**: R19–24.
20. Katz J, Kavanagh BP, Sandler AN. Effect of preoperative opioid administration on postoperative pain. *British Journal of Anaesthesia* 1992; **69**: 424.
21. Woolf CJ, Wall PD. Morphine-sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. *Neuroscience Letters* 1986; **64**: 221–225.
22. McQuay HJ. Pre-emptive analgesia. *British Journal of Anaesthesia* 1992; **69**: 1–3.
23. Pryle BJ, Vanner RG, Enriquez N, Reynolds F. Can pre-emptive lumbar epidural blockade reduce postoperative pain following lower abdominal surgery? *Anaesthesia* 1993; **48**: 120–123.
24. Tverskoy M, Yuval O, Isakson A, Finger J, Bradley EL, Kissin I. Preemptive effect of fentanyl and ketamine on postoperative pain and wound hyperalgesia. *Anesthesia and Analgesia* 1994; **78**: 205–209

British Journal of Anaesthesia 1996; **76**: 77–80

Prilocaine 3% is superior to a mixture of bupivacaine and lignocaine for peribulbar anaesthesia

U. R. DÖPFMER, D. G. MALONEY, P. A. GAYNOR, R. M. H. RATCLIFFE AND S. DÖPFMER

Summary

We have compared motor block of the extraocular muscles produced by injections of 3% prilocaine and a mixture of equal parts of 2% lignocaine and 0.75% bupivacaine into the medial compartment of the orbit. A volume of 8 ml was used initially, and a vasoconstrictor and hyaluronidase were added to both solutions. Ninety patients undergoing cataract surgery were allocated randomly to one of two groups in a double-blind study. Eight minutes after block insertion, the median ocular movement score in the prilocaine group was 1 and in the lignocaine–bupivacaine group 3. This difference was statistically significant ($P = 0.016$). Twenty of the patients who received prilocaine and 29 of the patients who received the lignocaine–bupivacaine mixture required an additional inferotemporal injection. This difference was not statistically significant ($P = 0.094$). (*Br. J. Anaesth.* 1996; **76**: 77–80)

Key words

Anaesthetic techniques, regional, peribulbar. Anaesthetics local, prilocaine. Anaesthetics local, bupivacaine. Anaesthetics local, lignocaine.

In our opinion, regional anaesthesia is the technique of choice for the vast majority of patients undergoing cataract surgery. Peribulbar anaesthesia seems to be safer than injections inside the extraocular muscle cone, especially when non-ophthalmologists perform the block [1,2].

Many modifications of the peribulbar technique have been described since the original report of Davis [3]. These include a variety of points of needle entry, direction and depth of needle insertion and of number of injections made [4].

A mixture of bupivacaine and lignocaine is the local anaesthetic used most frequently. Hyaluronidase and adrenaline are commonly added in varying concentrations to this mixture. Prilocaine has been used successfully for regional ocular anaesthesia [5, 6]. We are not aware of any formal comparison of prilocaine and a mixture of bupivacaine and lignocaine for peribulbar anaesthesia. In the UK preservative-free prilocaine in a concentration of 3% is available only in combination with felypressin. We added hyaluronidase to this solution and compared it with a combination of lignocaine, bupivacaine, hyaluronidase and adrenaline using a single injection into the medial compartment of the orbit.

Patients and methods

The local medical Ethics Committee gave approval for the study, and 90 patients presenting for cataract surgery under local anaesthesia gave informed consent. The sample size was determined on the basis of power calculation [7]. This study had a 95% chance of detecting a statistically significant (at the 5% level) true difference of 2 points for the sums of the eye movement scores.

Patients were allocated randomly to group 1 or 2. Group 1 received a mixture of equal volumes of 2% lignocaine and 0.75% bupivacaine, with adrenaline 5 $\mu g\ ml^{-1}$ and hyaluronidase 75 u. ml^{-1} (the mixture group). Group 2 received 3% prilocaine, with felypressin 0.03 u. ml^{-1} (Citanest with Octapressin, Astra) and hyaluronidase 75 u. ml^{-1} (the prilocaine group).

Randomization was performed in blocks of 10, using statistical tables for permutated blocks. The block size was not known by the investigators. Allocation was undertaken using sealed envelopes, which were not handed over to the clinician performing the blocks, but to an anaesthetist not involved in the trial, who then drew up the local anaesthetic mixture and handed the unlabelled syringe to the investigator.

All patients were assessed before operation; they were not premedicated and not fasted. On arrival in the anaesthetic room analgesia of the conjunctiva and cornea was provided by administering 2–3 drops of 1% amethocaine topically, twice within 2 min. In the interval between these two doses a vein was cannulated and arterial pressure measured with an automated oscillometer; monitoring of arterial oxygen saturation and the ECG was commenced. Approximately 1 min after the last dose of amethocaine eye drops, injection into the medial compartment of the orbit was carried out. A 25-gauge, 25-mm hypodermic needle was inserted just medial to the caruncle. The needle was introduced along the medial wall of the orbit to a depth of 20–25 mm. The sharp bevel was facing the globe. The direction of

---

U. R. DÖPFMER*, MD, DEAA, FRCA, D. G. MALONEY, MB, CHB, P. A. GAYNOR, MB, BS, FRCA, R. M. H. RATCLIFFE, MB, CHB, FRCA, Department of Anaesthesia, East Surrey Hospital, Three Arch Road, Redhill, Surrey RH1 5RH. S. DÖPFMER, MD, MSC, Institut für Medizinische Statistik, Universitätsklinikum Benjamin Franklin, Hindenburgdamm 30, 12200 Berlin, Germany.

Accepted for publication: August 3 1995.

*Present address for correspondence: Kreuzbergstrasse 30, D-10965 Berlin, Germany.

Table 1 Scoring system for degree of akinesia

Ocular movements	
Full movement	3
Moderate movement	2
Flicker	1
No movement	0
Eyelid movement	
Full movement	2
Flicker	1
No movement	0

insertion was almost perpendicular to the frontal and parallel to the sagittal plane; the eye was in the neutral position. After gentle negative aspiration, 8 ml of solution was injected over 30–40 s. A similar technique has been described by Brahma and co-workers [6]. Manual massage and gentle compression of the eyeball was performed for the first 2 min after this injection. Between scoring, a Honan balloon inflated to a pressure of 30 mm Hg was applied.

Globe movement was scored for each direction of gaze, as shown in table 1 [6]. The maximum score for each direction at any time was 3 points, the maximum sum 12 points. The scoring system for eyelid movements is also shown in table 1. Globe and eyelid movements were assessed at 2, 4, 6 and 8 min and thereafter every 2 min up to 16 min, if the block was considered inadequate for surgery 8 min after the first injection. If the block was still not sufficient at 10 min, another injection of the same drug was given.

Supplementary injections were given by the transconjunctival route with needle insertion at the lower margin of the orbit at the junction of the lateral and middle third. The needle was directed along the floor of the orbit to a depth of 20–25 mm; 2–5 ml of the solution used previously was injected after a negative aspiration test. The time when the operation started was noted.

Complications during or after injection were noted, and patients were asked after operation if they experienced any pain during surgery or while the block was inserted. Predefined summary measures [8] were the difference in median scores after 8 min, and the time needed to reach adequate block to start the operation. Data were analysed by Wilcoxon rank sum test. The need for top-up injections, the number of patients who reached an ocular movement score of 0 or 1 and complications were compared using the chi-square or Fisher's exact test, as appropriate.

Results

Patient characteristics in the two groups were similar (table 2).

Table 2 Baseline characters of patients (mean (SD or range) or number)

	Group 1	Group 2
n	46	44
Sex (M/F)	18/28	16/28
Age (yr)	75 (44–96)	76 (37–92)
Axial length (mm)	22.8 (1.2)	22.8 (1.0)

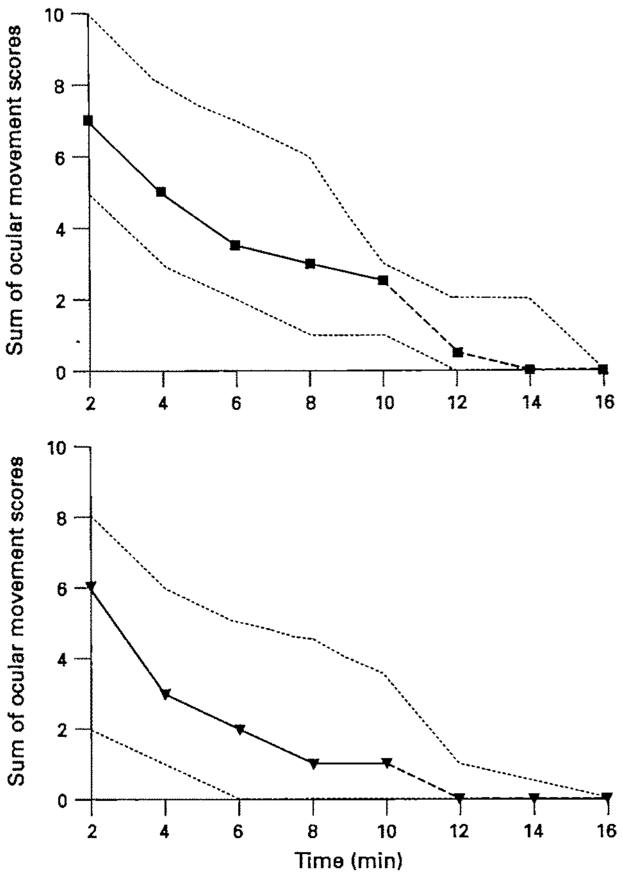


Figure 1 Sum of ocular movement scores (medians and interquartile ranges) over time in the lignocaine–bupivacaine (top) and prilocaine (bottom) groups. Required top-up injections were given at 10 min.

Complications during or after injection did not differ between the two groups (Fisher's exact test, $P = 0.714$). Seventeen patients in each group reported mild discomfort on inserting the block; significant conjunctival chemosis occurred in two patients in the mixture group, and four patients in the prilocaine group. This did not interfere with surgery. Subcutaneous haematoma formation occurred in three patients (two and one, respectively). Complications of a more serious nature were not noted. Only four patients reported intraoperative pain (three in the mixture group and one in the prilocaine group). One patient required additional topical anaesthesia with amethocaine drops, while the other three patients showed no signs of intraoperative distress, but reported minor pain on direct questioning immediately after operation. Eyelid movement was always blocked satisfactorily at 8 min. There was no significant difference in scores between the two groups ($P = 0.294$).

At 8 min the sum of the ocular movement scores was significantly lower in the prilocaine group (Wilcoxon rank sum test, P (two-sided) $= 0.0163$). The sums of the ocular movement scores over time are shown in figure 1. Ocular movement scores 8 min after injection are shown in figure 2.

Twelve patients in the mixture group and 27 patients in the prilocaine group had an ocular movement core of 0 or 1, 8 min after the medial injection (chi-square $= 11.4$, P (two-sided) < 0.001).

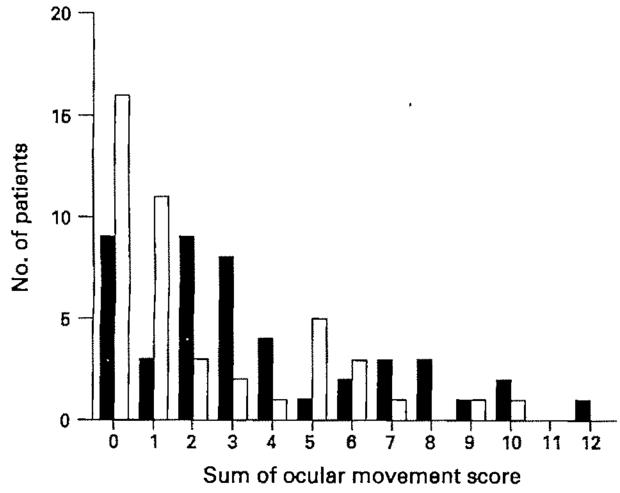


Figure 2 Distribution of the sums of the ocular movement scores 8 min after injection, for the lignocaine–bupivacaine (■) and the prilocaine (□) groups.

The median time at which the block was considered to be sufficient to start the operation was 12 min in the mixture group and 10 min in the prilocaine group (*P* (two-sided) = 0.091). Twenty-nine (63 %) patients in the mixture group and 20 (45.5 %) in the prilocaine group needed supplementary injections because the block was still not adequate at 10 min, a difference which did not reach statistical significance (chi-square = 2.81, *P* (two-sided) = 0.094). The insertion of top-up injections was completely pain-free in all patients.

Discussion

We have shown that prilocaine provided better ocular akinesia within the first 10 min after block insertion than a lignocaine–bupivacaine mixture when used for peribulbar block in combination with a vasopressor and hyaluronidase.

We deliberately chose a single injection into the medial compartment, as a high success rate has been reported previously for this technique [6]. Furthermore, we considered a single injection technique to be more likely to reveal an inherent difference between the spread of the agents throughout the orbit. The medial entry site for the needle was chosen because it is our experience that this injection causes much less discomfort than the inferotemporal approach, no matter whether the latter is performed through a transdermal or a transconjunctival route.

Our re-block rate in both groups was higher than in previously reported studies [6, 9–11], perhaps because we strived for almost complete ocular akinesia as the majority of patients were operated on without the use of holding stitches to avoid post-operative astigmatism. Despite this, we still advocate the technique described. The only alteration that we have made for routine cases is that assessment of the need for additional injections is made 6 min after the initial block. By that time analgesia of the inferotemporal part of the globe and orbit is well established, and an additional injection at this site is completely pain-free and abolishes residual downward and lateral eye movement within a short time.

Many scoring systems have been used for ocular range of movement [6, 12–14]. All of these are subjective, and commonly only sum scores incorporating all directions of gaze are reported, although it is obvious that major movement in only one direction is more disruptive to surgery than minor movement in two or more directions. Therefore, usually sum scores and re-block rates are reported simultaneously. An accurate, objective method of measuring eye movement that is easily performed in the anaesthetic room would greatly facilitate research in this field.

We did not study the duration of anaesthesia and analgesia provided by prilocaine, but patients never experienced pain towards the end of surgery, despite delays of up to 1.5 h in the operating programme.

We chose to add a large dose of hyaluronidase to the local analgesic solution as we wished to take advantage of any possible effects promoting spread. There is conflicting evidence on whether or not hyaluronidase improves the onset time or final akinesia achieved in double injection peribulbar blocks with lignocaine and bupivacaine [11, 13, 15]. Further studies are needed to determine if hyaluronidase is a useful addition to prilocaine when used for the technique described.

It would also be interesting to determine if the lignocaine–bupivacaine mixture would eventually have reached the same degree of extraocular muscle block had no further injections been given after 10 min. This study did not establish whether there is purely a difference in time of onset, or a true difference in maximum motor block, achieved with the two solutions.

References

1. Lichter PR. The relative value of quality care. *Ophthalmology* 1991; **98**: 1151–1152.
2. Grizzard WS, Kirk NM, Pavan PR, Antworth MV, Hammer ME, Rosemann RL. Perforating ocular injuries caused by anesthesia personnel. *Ophthalmology* 1991; **98**: 1011–1016.
3. Davis DB. Posterior peribulbar anesthesia. *Journal of Cataract and Refractive Surgery* 1986; **12**: 128–134.
4. Fry RA, Henderson J. Local anaesthesia for eye surgery. *Anaesthesia* 1989; **45**: 14–17.
5. Saunders DC, Sturgess DA, Pemberton CJ, Morgan LH, Bourne A. Peribulbar and retrobulbar anesthesia with prilocaine: a comparison of two methods of local ocular anaesthesia. *Ophthalmic Surgery* 1993; **24**: 842–845.
6. Brahma AK, Pemberton CJ, Ayeko M, Morgan LH. Single medial injection peribulbar anaesthesia using prilocaine. *Anaesthesia* 1994; **49**: 1003–1005.
7. Pocock SJ. Sample size calculations. In: Pocock SJ, ed. *Clinical Trials: A Practical Approach*. Chichester: John Wiley & Sons, 1989; 123–141.
8. Matthews JNS, Altmann DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *British Medical Journal* 1990; **300**: 230–235.
9. Whitsett JC, Balyeat HD, McClure B. Comparison of one-injection-site peribulbar anesthesia and retrobulbar anesthesia. *Journal of Cataract and Refractive Surgery* 1990; **16**: 243–245.
10. Zahl K, Jordan A, McGroarty J, Sorenson B, Gotta AW. Peribulbar anesthesia. Effect of bicarbonate on mixtures of lidocaine, bupivacaine, and hyaluronidase with or without epinephrine. *Ophthalmology* 1991; **98**: 239–242.
11. Crawford M, Kerr WJ. The effect of hyaluronidase on peribulbar block. *Anaesthesia* 1994; **49**: 907–980.
12. Hamilton RC, Gimbel HV, Strunin L. Regional anaesthesia

for 12,000 cataract extraction and intraocular lens implantation procedures. *Canadian Journal of Anaesthesia* 1988; 35: 615–623.

13. House PH, Hollands RH, Schulzer M. Choice of anesthetic agents for peribulbar anesthesia. *Journal of Cataract and Refractive Surgery* 1991; 17: 80–83
14. Nicoll JMV, Treuren B, Acharya PA, Ahlen K, James M. Retrobulbar anesthesia: the role of hyaluronidase. *Anesthesia and Analgesia* 1986; 65: 1324–1328.
15. Morsmann CD, Holden R. The effects of adrenaline, hyaluronidase and age on peribulbar anaesthesia. *Eye* 1992; 6: 290–292.

British Journal of Anaesthesia 1996; **76**: 81–84

Haemodynamic effects of moderate normovolaemic haemodilution in conscious and anaesthetized patients

P. Biboulet, X. Capdevila, D. Benetreau, P. Aubas, F. d'Athis and J. du Cailar

Summary

We have assessed the haemodynamic effects of moderate normovolaemic haemodilution in ASA I patients, either conscious or during enflurane–fentanyl anaesthesia (10 patients in each group). Cardiac index (CI), stroke index (SI) and ejection fraction (EF) were measured by transthoracic electrical bioimpedance and, in the anaesthesia group, arterial and central venous blood samples were obtained to assess oxygen delivery ($D\mathrm{O}_2$), oxygen consumption ($\dot{V}\mathrm{O}_2$) and oxygen extraction ratio (O_2ER). In conscious patients, heart rate (HR) remained unchanged as SI, EF and CI increased. When haemodilution was performed during anaesthesia, CI remained stable in spite of a slight increase in SI, as HR decreased. This produced a reduction in $D\mathrm{O}_2$ which was compensated for by an increase in O_2ER, allowing maintenance of $\dot{V}\mathrm{O}_2$ without alteration in blood lactate concentration. (*Br. J. Anaesth.* 1996; **76**: 81–84)

Key words

Blood, haemodilution. Measurement techniques, transthoracic electrical impedance. Cardiovascular system, effects.

Preoperative acute isovolaemic haemodilution is commonly used to avoid the adverse consequences of homologous blood transfusion [1]. Moderate haemodilution, defined by a decrease in packed cell volume (PCV) of approximately 30% [2] has been shown to be relatively safe, as the decrease in arterial oxygen content is compensated for by an increase in cardiac output, maintaining oxygen delivery. The increase in cardiac output results from an increase in stroke volume rather than heart rate [3–6] and occurs in response to a decrease in blood viscosity and increased myocardial contractility [7, 8]. The reduction in blood viscosity plays a fundamental role by decreasing myocardial afterload [4] and increasing venous return [9]. In order to explain the increased myocardial contractility, an increase in sympathetic tone has been suggested [10], mediated by baroreceptors and chemoreceptors [11]. In contrast with these data obtained from studies performed under light anaesthesia [3, 5, 6], an increase in cardiac output during haemodilution does not occur during neuroleptanalgesia [12] or during enflurane–nitrous oxide anaesthesia [13]. As most anaesthetic agents decrease myocardial contractility and venous return, they might attenuate the haemodynamic response to acute haemodilution. However, these two studies were performed in elderly patients [12] or in patients with cardiovascular disease, or both [13], factors which may compromise the cardiovascular changes occurring during haemodilution.

The aim of this study was to assess the haemodynamic changes after normovolaemic haemodilution in ASA I patients, either conscious or under anaesthesia, in order to examine the effect of anaesthetic agents on the cardiovascular response.

Patients and methods

The study was approved by the local Ethics Committee and informed consent was obtained from each patient.

CONSCIOUS PATIENTS

We studied 10 consecutive ASA I patients, aged 23–48 yr, undergoing orthopaedic surgery. Haemodilution was performed the day before surgery in unpremedicated patients. The blood volume to be withdrawn to achieve a PCV of about 30% was calculated from basal PCV levels using a chart. Blood was collected into standard citrate–phosphate–glucose blood storage bags and replaced simultaneously by i.v. administration of an equal volume of dextran 60 (Hemodex). The characteristics of this colloid are: 6% concentration, molecular weight of approximately 60000 Da and oncotic pressure 7.46 kPa. The likelihood of an anaphylactic reaction was reduced by hapten inhibition with dextran 1000 (Promit) 3 g.

PCV was measured using the micromethod (Compur M 1101, Compur Electronic GmbH, Munich, Germany) before, during and 5 min after haemodilution. Heart rate (HR) was measured from an electrocardiogram and mean arterial pressure (MAP) using an automated method (Trend BP 5000, Colin Electronics Co. Ltd, Japan). Cardiac index (CI), stroke volume index (SI) and left ventricular

---

Philippe Biboulet*, md, Xavier Capdevila, md, msc, Didier Benetreau, md, Françoise d'Athis, md, Jacques du Cailar, md (Department of Anaesthesiology and Intensive Care A); Pierre Aubas, md (Department of Medical Information); University Hospital, Montpellier, France. Accepted for publication: July 17, 1995.

*Address for correspondence: Department of Anaesthesiology A, Hôpital Lapeyronie, 371, avenue du Doyen Giraud, 34295 Montpellier Cédex 5, France.

ejection fraction (EF) were measured or calculated non-invasively by transthoracic electrical bio-impedence (TEB) using the Bomed NCCOM3 with software version R-7 (Bomed Medical Manufacturing Ltd, Irvine, CA, USA). For TEB data, three recordings were averaged over the time taken to record arterial pressure. Haemodynamic variables were measured at rest, before haemodilution (T0) and 5 min after (T1).

ANAESTHETIZED PATIENTS

We studied 10 consecutive ASA I patients, aged 18–55 yr, undergoing major elective orthopaedic surgery with haemodilution. Patients received midazolam 0.1 mg kg^{-1} i.m. as premedication. Anaesthesia was induced, without preloading, with fentanyl 5 μg kg^{-1}, thiopentone 5 mg kg^{-1} and vecuronium 0.1 mg kg^{-1}, and maintained with fentanyl 0.08 μg kg^{-1} min^{-1} and 0.8% enflurane. After tracheal intubation, patients' lungs were ventilated with 50% nitrous oxide in oxygen and tidal volume was adjusted to maintain end-tidal carbon dioxide values of 4.5 kPa.

Cannulae were inserted in a radial artery and the right internal jugular vein. Normovolaemic haemodilution was performed as described previously, after induction and insertion of the cannulae. PCV and haemodynamic variables (HR, MAP, CI; SI and EF) were measured using the same method as in the conscious group. Additionally, central venous pressure was measured and arterial and central venous blood samples were obtained to measure arterial oxygen content (Ca_{O_2}), central venous oxygen content (Ccv_{O_2}) and arterial blood lactate concentration. Blood samples were analysed immediately using an automated system for blood gases (Radiometer ABL 330, Radiometer CO, Copenhagen, Denmark). Oxygen saturation, haemoglobin (Radiometer OSM2, Radiometer CO, Copenhagen, Denmark) and blood lactate concentrations (enzymatic method) were measured also. Oxygen delivery (Do_2), oxygen consumption ($\dot{V}o_2$) and oxygen extraction ratio (O_2ER) were calculated with standard formulae using central venous data instead of mixed venous measurements. Haemodynamic measurements were performed and blood samples obtained just before haemodilution (T0) and 5 min after (T1).

Table 1 Patient characteristics (mean (range or SD))

	Age (yr)	Height (m)	Weight (kg)
Conscious patients	38 (23–48)	1.74 (0.11)	69 (14)
Anaesthetized patients	36 (18–55)	1.71 (0.07)	69 (11)

STATISTICS

Data are expressed as mean (SD). Statistical analysis was performed using the Wilcoxon test. The level of significance was defined as $P < 0.05$.

Results

CONSCIOUS PATIENTS

Haemodilution was performed in three women and seven men (table 1). The mean volume of blood withdrawn was 1058 (261) ml over a period of 49 (16) min. PCV decreased from 41 (4) % at T0 to 30 (1) % at T1 ($P < 0.05$). After haemodilution, SI, EF and CI increased as HR and MAP remained unchanged (table 2).

ANAESTHETIZED PATIENTS

Haemodilution was performed in three women and seven men (table 1). The mean time from induction of anaesthesia to haemodilution (T0) was 54 (5.8) min. The mean volume of blood withdrawn was 926 (294) ml over 38 (10) min. PCV decreased from 38 (3)% at T0 to 29 (2)% at T1 ($P < 0.05$), corresponding to a decrease in arterial haemoglobin from 12.4 (1) g 100 ml^{-1} to 9.5 (0.6) g 100 ml^{-1} ($P <$ 0.05). After normovolaemic haemodilution, MAP and HR decreased, SI and EF increased, as CI and CVP remained unchanged (table 3). Ca_{O_2} and Do_2 decreased considerably, central venous saturation (Scv_{O_2}) decreased while $\dot{V}o_2$ did not change significantly and O_2ER increased. Blood lactate concentrations remained unchanged and Pa_{CO_2} remained stable (table 4).

Discussion

We have shown that the haemodynamic effects of moderate normovolaemic haemodilution were different in conscious and anaesthetized ASA I patients. When haemodilution was performed on conscious patients, the classic haemodynamic response described previously [3–6] was observed. The significant increase in CI resulted from an increase in SI as HR remained unchanged; the increase in SI was related to the increase in EF. Conversely, when haemodilution was performed under anaesthesia, CI remained stable, in spite of a slight increase in SI, as HR decreased. This produced a reduction in Do_2 compensated for by an increase in O_2ER which induced a decrease in $ScvO_2$. This metabolic response allows maintenance of $\dot{V}o_2$ without alteration in blood lactate concentration, evidence of adequate global tissular oxygenation.

In this study, we used the non-invasive bio-

Table 2 Haemodynamic changes after haemodilution in conscious patients. Comparison between mean arterial pressure (MAP), heart rate (HR), stroke volume index (SI), cardiac index (CI) and ejection fraction (EF), measured before (T0) and 5 min after (T1) normovolaemic haemodilution (mean (SD)). $^{**}P < 0.01$

	MAP (mm Hg)	HR (beat min^{-1})	SI (ml m^{-2})	CI (litre min^{-1} m^{-2})	EF (%)
T0	93 (11)	83 (9)	44 (11)	3.6 (0.9)	62 (8)
T1	93 (12)	87 (11)	51 (11)**	4.5 (1.2)**	68 (4)**

Table 3 Haemodynamic changes after haemodilution performed under general anaesthesia. Comparison between mean arterial pressure (MAP), central venous pressure (CVP), heart rate (HR), stroke volume index (SI), cardiac index (CI) and ejection fraction (EF), measured before (T0) and 5 min after (T1) normovolaemic haemodilution (mean (SD). $^*P < 0.05$

	MAP (mm Hg)	CVP (mm Hg)	HR (beat $\min^{-1}$)	SI (ml m^{-2})	CI (litre $\min^{-1}$ m^{-2})	EF (%)
T0	74 (5)	4.6 (3.3)	61 (12)	33 (5)	2 (0.4)	50 (7)
T1	70 (5)*	4.7 (3.2)	58 (10)*	34 (5)*	2 (0.4)	55 (7)*

Table 4 Effects of haemodilution performed during general anaesthesia on arterial and central venous blood gases, arterial and central venous oxygen content (Ca_{O_2}, Ccv_{O_2}), oxygen delivery (Do_2), oxygen consumption ($\dot{V}o_2$), oxygen extraction ratio (O_2ER) and arterial blood lactate concentration (lactate). Comparison between values measured before (T0) and 5 min after (T1) normovolaemic haemodilution. $^*P < 0.05$, $^{**}P < 0.01$

	T0	T1
Pa_{O_2} (kPa)	29.4 (0.7)	30.3 (0.7)
Pa_{CO_2} (kPa)	4.4 (0.7)	4.5 (0.7)
Sa_{O_2} (%)	99.5 (0.3)	99.5 (0.3)
Ca_{O_2} (ml 100 ml^{-1})	17.3 (1.4)	13.5 (0.9)**
Do_2 (ml $\min^{-1}$ m^{-2})	345 (8)	268 (6)**
Pcv_{O_2} (kPa)	5.2 (0.5)	4.8 (0.5)*
Scv_{O_2} (%)	71.8 (3.8)	66.5 (5.9)*
Ccv_{O_2} (ml 100 ml^{-1})	12.1 (1.5)	8.7 (1.1)**
$\dot{V}o_2$ (ml $\min^{-1}$ m^{-2})	102.2 (18)	94.3 (20)
O_2ER (%)	30.1 (5)	35.4 (6)*
Lactate (mmol $litre^{-1}$)	1.9 (0.7)	2 (0.8)

impedance method [14], the accuracy of which has been controversial. In critically ill patients with water and electrolyte disorders, measurement of CI by TEB lacks precision [15–17] but the technique is accurate in normal subjects and in high risk surgical patients [18–21]. Measurement of EF by the TEB method has been validated also [22]. Changes in PCV have little influence on the calculation of CI by the Sramek formula used by the Bomed NCCOM3 [17, 23]. Blood obtained from the superior vena cava was used for measurement of venous oxygen saturation. However, adequate correlation between central venous and mixed venous oxygen saturation [24–26] has been questioned recently in critically ill patients [27–29].

Our findings agree with the study of Van der Linden and colleagues where CI remained stable, in spite of a slight increase in SI, as HR decreased when haemodilution was performed during enflurane–nitrous oxide anaesthesia [13]. This results in a significant decrease in Do_2; $\dot{V}o_2$ was maintained by an increase in O_2ER. The smaller increase in SI and the decrease in HR seem to be related to the inotropic and bradycardiac effects of the anaesthetic agents. Enflurane is known to have both a depressant effect on the myocardium [30, 31] and on cardiac conduction [32]. Vecuronium and thiopentone with or without fentanyl have been associated with significant bradycardia [33]. Cases where CI has failed to increase during moderate haemodilution have been described also during neuroleptanalgesia [12].

On the other hand, those studies which reported an increase in CI with maintenance of Do_2 during haemodilution were conducted in conscious patients [34] or using low concentrations of anaesthetic agents [3, 5, 6].

The metabolic repercussions of this inadequate haemodynamic response to acute anaemia when haemodilution is performed under anaesthesia are difficult to determine. It is unlikely that a global measure such as Do_2, $\dot{V}o_2$ or blood lactate concentration can predict adequately the responses of specific tissues to decreased oxygen delivery [35]. For example, haemodilution improves the microcirculation with more homogeneous distribution of capillary flow resulting in improvement in local oxygen supply [1]. Additionally, $\dot{V}o_2$ decreases during general anaesthesia. The myocardium is one of the principal organs at risk during haemodilution as O_2ER exceeds 50%; nevertheless, haemodilution is tolerated well in patients with coronary disease [4, 36, 37]. However, if oxygen demand increases, the magnitude of haemodilution may be inappropriate, which explains the higher incidence of postoperative cardiac ischaemia in atherosclerotic patients when PCV is less than 29% [38]. The major problem is during the recovery period when oxygen demand increases. A critical level of haemodilution is therefore difficult to define, particularly in patients with coronary artery disease [35, 39, 40].

In summary, we found that haemodynamic response to moderate normovolaemic haemodilution was impaired in ASA I patients during enflurane–fentanyl anaesthesia. $\dot{V}o_2$ was maintained by a corresponding increase in O_2ER. In high-risk patients this metabolic adaptation may be inadequate, resulting in a $\dot{V}o_2$ which is dependent on oxygen supply thus leading to local tissue ischaemia.

References

1. Messmer K, Kreimeier U, Intaglietta M. Present state of intentional haemodilution. *European Surgical Research* 1986; **18**: 254–263.
2. Messmer K. Hemodilution. *Surgical Clinics of North America* 1975; **55**: 659–678.
3. Lacks H, Pilon RN, Klovekorn WP, Anderson W, Mac Callum JR, O'Connor NE. Acute hemodilution: its effect on hemodynamics and oxygen transport in anesthetized man. *Annals of Surgery* 1974; **180**: 108–109.
4. Shah DM, Prichard MN, Newell JC, Karmody AM, Scovill WA, Powers SR. Increased cardiac output and oxygen transport after intraoperative isovolemic hemodilution. A study in patients with peripheral vascular disease. *Archives of Surgery* 1980; **115**: 597–600.
5. Rose D, Coutsoftides T. Intraoperative normovolemic hemodilution. *Journal of Surgical Research* 1981; **31**: 375–381.
6. Gisselsson L, Rosberg B, Ericsson M. Myocardial blood flow, oxygen uptake and carbon dioxide release of the human heart during haemodilution. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 589–591.

7. Murray JF, Escobar E, Rapaport E. Effects of blood viscosity on hemodynamic responses in acute normovolemic anemia. *American Journal of Physiology* 1969; **216**: 638–642.
8. Rodriguez JA, Chamarro GA, Rapaport E. Effect of isovolemic anemia on ventricular performance at rest and during exercise. *Journal of Applied Physiology* 1974; **36**: 28–33.
9. Guyton AC, Richardson TQ. Effect of hematocrit on venous return. *Circulation Research* 1961; **9**: 157–164.
10. Glick G, Plauth WH, Braunwald EB. Role of the autonomic nervous system in the circulatory response to acutely induced anemia in unanesthetized dogs. *Journal of Clinical Investigation* 1964; **43**: 2112–2124.
11. Hatcher JD Chiu LK, Jennings DB. Anemia as a stimulus to aortic and carotid chemoreceptors in the cat. *Journal of Applied Physiology* 1978; **44**: 696–702.
12. Rosberg B, Wulff K. Haemodynamics following normovolaemic haemodilution in elderly patients. *Acta Anaesthesiologica Scandinavica* 1981; **25**: 402–406.
13. Van der Linden P, Wathieu M, Gilbart E, Engelman E, Wautrecht JC, Lenaers A, Vincent JL. Cardiovascular effects of moderate normovolaemic haemodilution during enflurane–nitrous oxide anaesthesia in man. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 490–498.
14. Bernstein DP. Continuous noninvasive real-time monitoring of stroke volume and cardiac output by thoracic electrical bioimpedance. *Critical Care Medicine* 1986; **14**: 898–901.
15. Donovan KD, Dobb GJ, Woods WPD, Hockings BE. Comparison of transthoracic electrical impedance and thermodilution methods for measuring cardiac output. *Critical Care Medicine* 1986; **14**: 1038–1044.
16. Preiser JC, Daper A, Parquier JN, Contempré B, Vincent JL. Transthoracic electrical bioimpedance verus thermodilution technique for cardiac output measurement during mechanical ventilation. *Intensive Care Medicine* 1989; **15**: 221–223.
17. Woo MA, Hamilton M, Stevenson LW, Vredevoe DL. Comparison of thermodilution and transthoracic electrical bioimpedance cardiac outputs. *Heart and Lung* 1991; **20**: 357–362.
18. Northridge DB, Findlay IN, Wilson J, Henderson E, Dargie HJ. Non-invasive determination of cardiac output by Doppler echocardiography and electrical bioimpedance. *British Heart Journal* 1990; **63**: 93–97.
19. White SW, Quail AW, de Leeuw PW, Traugott FM, Brown WJ, Porges WL, Cottee DB. Impedance cardiography for cardiac output measurement: an evaluation of accuracy and limitations. *European Heart Journal* 1990; **11**: 79–92.
20. Wong DH, Tremper KK, Stemmer EA, O'Connor D, Wilbur S, Zaccari J, Reeves C, Weidoff P, Trujillo RJ. Noninvasive cardiac output: simultaneous comparison of two different methods with thermodilution. *Anesthesiology* 1990; **72**: 784–792.
21. Jewkes C, Sear JW, Verhoeff F, Sanders DJ, Foëx P. Non-invasive measurement of cardiac output by thoracic electrical bioimpedance: a study of reproducibility and comparison with thermodilution. *British Journal of Anaesthesia* 1991; **67**: 788–794.
22. Hanna L, Lopez-Majano V, Ward J, Mathew M, Aldrete JA. Non-invasive ejection fraction monitoring: a comparison of the impedance method to the radionuclide cardiography (abstract). *Anesthesiology* 1988; **69**: A308.
23. Thomas A, Vohra A, Pollard B. The effect of haematocrit on transthoracic electrical impedance and on the calculation of cardiac output by an impedance cardiograph. *Intensive Care Medicine* 1991; **17**: 178–180.
24. Scheinman MM, Brown MA, Rapaport E. Critical assessment of use of central venous oxygen saturation as a mirror of mixed venous oxygen in severely ill cardiac patients. *Circulation* 1969; **40**: 165–172.
25. Tahvanainen J, Meretoja O, Nikki P. Can central venous blood replace mixed venous blood samples? *Critical Care Medicine* 1982; **10**: 758–761.
26. Berridge JC. Influence of cardiac output on the correlation between mixed venous and central venous oxygen saturation. *British Journal of Anaesthesia* 1992; **69**: 409–410.
27. Martin C, Auffray JP, Badetti C, Perrin G, Papazian L, Gouin F. Monitoring of central venous oxygen saturation versus mixed venous oxygen saturation in critically ill patients. *Intensive Care Medicine* 1992; **18**: 101–104.
28. Vincent JL. Does central venous oxygen saturation accurately reflect mixed venous oxygen saturation? Nothing is simple, unfortunately. *Intensive Care Medicine* 1992; **18**: 386–387.
29. Rigg JD, Nightingale PN, Faragher EB. Influence of cardiac output on the correlation between mixed venous and central venous oxygen saturation. *British Journal of Anaesthesia* 1993; **71**: 459.
30. Merin RG, Kumazawa T, Luka NL. Enflurane depresses myocardial function, perfusion and metabolism in the dog. *Anesthesiology* 1976; **45**: 501–507.
31. Housmans PR, Murat I. Comparative effects of halothane, enflurane and isoflurane at equipotent anesthetic concentration on isolated ventricular myocardium of the ferret. I. contractility. *Anesthesiology* 1988; **69**: 451–463.
32. Bosnjak ZJ, Kampine JP. Effects of halothane, enflurane, and isoflurane on the SA node. *Anesthesiology* 1983; **58**: 314–321.
33. Inoue K, El Banayosy A, Stolarski L, Reichelt W. Vecuronium induced bradycardia following induction of anaesthesia with etomidate or thiopentone, with or without fentanyl. *British Journal of Anaesthesia* 1988; **60**: 10–17.
34. Baron JF, de Kegel D, Prost AC, Mundler O, Arthaud M, Basset G, Maistre G, Masson F, Carayon A, Landault C, Barre E, Viars P. Low molecular weight hydroxyethyl starch 6% compared to albumin 4% during intentional hemodilution. *Intensive Care Medicine* 1991; **17**: 141–148.
35. Leone BJ, Spahn DR. Anemia, hemodilution and oxygen delivery. *Anesthesia and Analgesia* 1992; **75**: 651–653.
36. Catoire P, Saada M, Liu N, Delaunay L, Rauss A, Bonnet F. Effect of preoperative normovolemic hemodilution on left ventricular segmental wall motion during abdominal aortic surgery. *Anesthesia and Analgesia* 1992; **75**: 654–659.
37. Spahn DR, Smith LR, McRae RL, Leone BJ. Effects of acute isovolemic hemodilution and anesthesia on regional function in left ventricular myocardium with compromised coronary blood flow. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 628–636.
38. Christopherson R, Frank S, Norris E, Rock P, Gottlieb S, Beattie C. Low postoperative hematocrit is associated with cardiac ischemia in high-risk patients. *Anesthesiology* 1991; **75**: A99.
39. Leone BJ. Advantages and dangers of hemodilution in cardiac disease. *Current Opinion in Anesthesiology* 1993; **6**: 66–71.
40. Kettler D. "Permissive anemia" compared with blood transfusion in patients with cardiac disease: another point of view. *Current Opinion in Anesthesiology* 1994; **7**: 1–4.

British Journal of Anaesthesia 1996; **76**: 85–89

Analysis of ethanol in expired air during low-flow isoflurane anaesthesia

J. OLSSON AND R. G. HAHN

Summary

Monitoring of ethanol concentration in expired air is a method for assessing fluid absorption during transurethral prostatic surgery and endometrial resection, but the validity of this technique has not been studied in low-flow ventilation systems. For this purpose, we have compared the concentration–time profiles of ethanol in expired gas and in venous blood during an i.v. infusion of 0.4 g kg^{-1} of ethanol over 30 min in 10 women during isoflurane anaesthesia and in the awake state. Anaesthesia increased the ethanol concentration in expired gas by 13% and in venous blood by 34%. The expired gas–blood difference during infusion was abolished, and the central volume of distribution for ethanol was reduced from 20.9 to 8.6 litre, on average. We conclude that breath sampling during low-flow isoflurane anaesthesia reflects an alcohol load well, but that a change in ethanol disposition makes the values slightly higher than in the awake state. (*Br. J. Anaesth.* 1996; **76**: 85–89)

Key words

Anaesthetics volatile, isoflurane. Ethanol. Pharmacokinetics.

Measurement of ethanol in expired gas is performed most frequently in awake subjects who are suspected of driving offences in relation to drinking alcohol. In recent years, ethanol analysis in expired gas has been used as a marker of fluid absorption during transurethral resection of the prostate [1,2] and transcervical resection of the endometrium [3,4]. Ethanol monitoring was developed originally for spontaneously breathing patients under regional anaesthesia, but it has also been used under general anaesthesia [5,6]. However, atelectasis and hypothermia would be expected to give lower values for ethanol in the breath [7] while tracheal intubation may increase them by reducing the reabsorption of ethanol in the oral cavity during expiration [6].

The aim of the present study was to evaluate the validity of measurement of ethanol in expired gas during isoflurane anaesthesia using a low-flow breathing system. This was done by comparing ethanol concentrations and pharmacokinetics of ethanol in blood and expired gas during and after an i.v. infusion of ethanol during surgery. The experiment was repeated on the same subjects in the awake state.

Patients and methods

We studied 10 healthy women, aged 24–62 (mean 44) yr and with a body weight of 50–83 (mean 67) kg. They were consecutive patients admitted for elective ENT surgery with an estimated duration of more than 2 h. The study was approved by the local Ethics Committee and all patients gave informed consent to participate in two studies, one during general anaesthesia and one in the awake state about 2–6 weeks later.

In the first study, subjects were premedicated with triazolam 0.25 mg by mouth. General anaesthesia was induced with thiopentone and fentanyl, followed by atracurium or vecuronium. The lungs were ventilated using a circuit system (Q-system, Anmedic AB, Vallentuna, Sweden) with a bag-in-bottle, soda lime absorber and a heat and moisture exchanger (Humid-Vent 2 Port, Gibeck Respiration AB, Upplands Väsby, Sweden) with isoflurane and nitrous oxide in oxygen. After preoxygenation and denitrogenation for 5 min, a fresh gas flow of 6 litre min^{-1} was used during the first 5 min after tracheal intubation. During steady-state ventilation, the fresh gas flow was reduced to 1.5 litre min^{-1}. Body temperature was measured by an oesophageal probe (Datex/Instrumentarium Oy, Helsinki, Finland).

After general anaesthesia had been induced, we administered 0.4 g kg^{-1} of ethanol at a constant rate over 30 min by infusing a solution containing 10% ethanol and 5% glucose (w/v) with an infusion pump (Ivac 560, Ivac Co., San Diego, CA, USA) through a venous cannula placed in one arm.

Starting from the onset of infusion, concentrations of ethanol in blood and expired gas were measured at 20 exactly timed occasions over 2 h. Venous blood was sampled from a cannula placed in the arm opposite to that used for infusion and ethanol concentration was measured by gas chromatography (GC 6000 Vega Series 2, Carlo Erba Instruments, Milan, Italy). To avoid the "salting-out" effect of sodium fluoride used as an anticoagulant for whole blood [8], we analysed plasma samples and converted the ethanol concentration to whole blood data based

---

JOEL OLSSON, MD, Department of Anaesthesia, Sundsvall Central Hospital, S-851 86 Sundsvall, Sweden. ROBERT G. HAHN, MD, PHD, Department of Anaesthesia, Stockholm Söder Hospital, S-118 83 Stockholm, Sweden. Accepted for publication: August 7, 1995.

Correspondence to R.H.

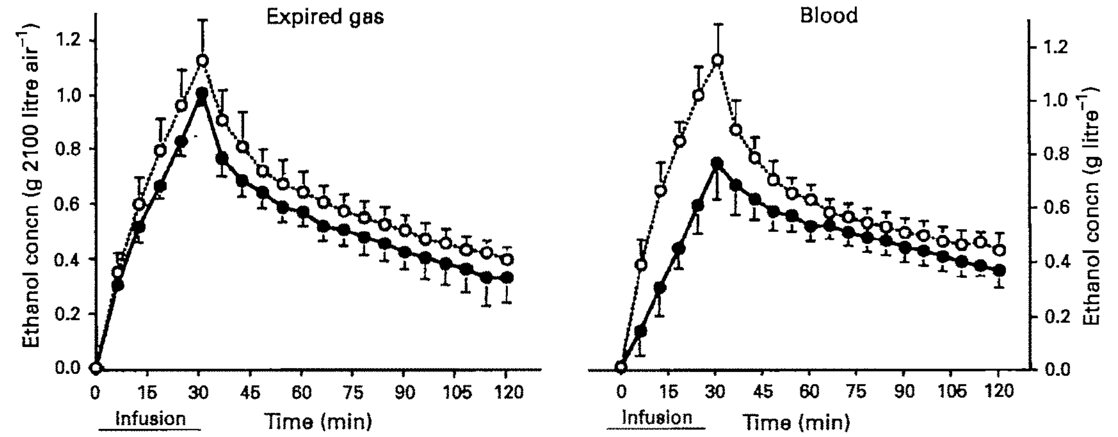


Figure 1 Expired gas and blood ethanol concentrations during i.v. infusion of 0.4 g kg^{-1} of ethanol in 10 women during isoflurane anaesthesia (○) and in the awake state (●) (mean, SD).

on a plasma–whole blood ratio of 1.10 [9]. Each sample was analysed twice and the mean value obtained. Duplicate analyses ensured a coefficient of variation of 1.7 %.

Ethanol concentration in expired gas was measured by a fuel cell type alcohol sensor (Alcolmeter S-D2, Lion Laboratories Ltd, S. Glamorgan, Wales). The breathalyser was calibrated by alcohol-in-gas standards before each study. To facilitate comparison with the blood ethanol concentration, the Alcolmeter readings were expressed in grams per 2100 litre of air. Accuracy was within 0.01 g per 2100 litre of air. Before each measurement, fresh gas flow was shut off by closing the circuit for 30 s. A 1.5-ml sample of air was taken at the end of passive expiration by attaching the Alcolmeter to an adapter placed between the tracheal tube and the heat and moisture exchanger of the ventilation system [6].

The second study was also performed at the hospital and followed the same design for ethanol infusion and plasma sampling as the first. The patient was conscious and no drug other than alcohol was given. She was instructed to take a deep breath and to blow into the mouthpiece of the Alcolmeter. Body temperature was measured by an earprobe (First Temp Genius 3000 A, Sherwood Medical, Carlsbad, CA, USA) which was calibrated to show the same values as the oesophageal probe.

In five patients where the operation ended earlier than expected, only data obtained during low-flow anaesthesia (mean 15.5) are reported. The corresponding measurements obtained during the second experiment were also discarded. This allowed comparisons between the anaesthetized and awake patients to be made at all times.

To avoid problems associated with computing the variance of a ratio, the blood–expired gas partition coefficient of ethanol was calculated as the difference between logarithm-transformed individual expired gas and blood ethanol values. The data were converted to the original scale and then multiplied by 2100.

The pharmacokinetics of ethanol were studied by assuming that the ethanol concentration equals the sum of a first-order distribution function and a zero-order saturated Michaelis–Menten elimination function. The concentration (C) at any time after a bolus injection of ethanol was obtained as [10];

$$C = A\mathrm{e}^{-\alpha t} + B - \beta t$$

where α = first-order exponential rate constant, β = zero-order elimination rate constant and t = time after the start of infusion. A and B = concentrations of ethanol obtained when the first-order and the zero-order functions are extrapolated back to $t = 0$.

We curve-fitted the data by considering the effect of an i.v. infusion on the model variables according to the following equations [11]:

During infusion:

$$C = (A/\alpha T)(1-\mathrm{e}^{-\alpha t}) + (Bt/T) - \beta t$$

After infusion:

$$C = A[(1-e^{-\alpha T})/\alpha T]\,\mathrm{e}^{-\alpha(t-T)} + (B - \beta t)$$

where T = infusion time.

The model variables were estimated by using a non-linear curve fitting program for a digital computer (Model-PK, McPherson Scientific, Rosanna, Victoria, Australia). No weighting factor was used as the error in the blood-ethanol analysis was constant within the concentration range studied. The ethanol values were consistently higher than the Michaelis constant for alcohol dehydrogenase, which is 0.05–0.10 g litre^{-1} [12].

The volume of the central compartment (V_c) was obtained from the dose of ethanol divided by the sum of A and B. The total distribution volume (V^{extrap}) was obtained from the dose divided by B [13].

Results are presented as mean (SD). The area under the concentration–time curve for ethanol (AUC) during the experiment was calculated by the linear trapezoidal method. The statistical calculations were performed on a Macintosh computer using StatView 4.01 (Abacus Concepts, Berkeley, CA, USA). Differences were evaluated by the paired t test and Wilcoxon's matched pair test, as appropriate, and reported to be significant when $P < 0.05$.

Results

The ethanol concentration in expired air was 13 % higher during general anaesthesia than in the awake

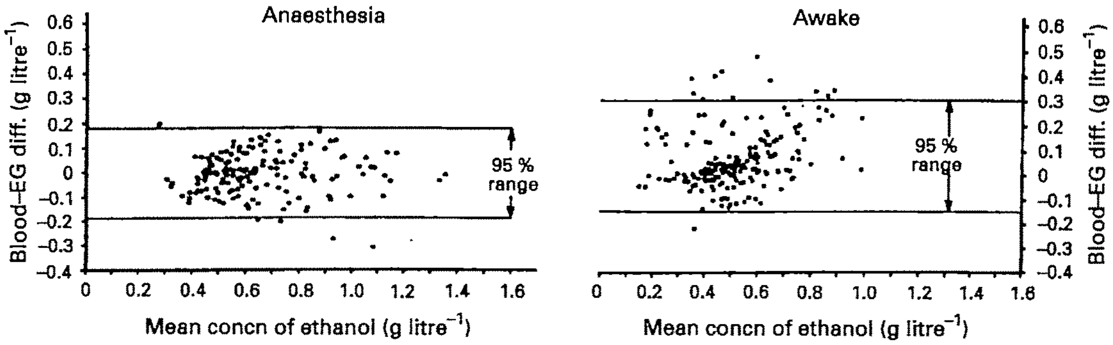


Figure 2 Agreement between ethanol concentrations in expired gas (EG) (× 2100) and blood in experiments with ethanol infusions during general anaesthesia (mean difference −0.005 (0.085)) ($n = 156$) and in the awake state (mean difference 0.062 (0.120)) ($n = 190$).

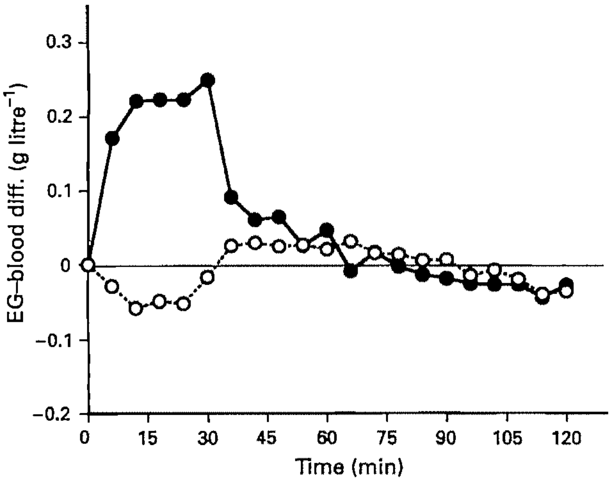


Figure 3 Expired gas (EG)–blood difference in ethanol concentration during and after i.v. infusion of ethanol during isoflurane anaesthesia (○) and in the awake state (●) (mean). Ethanol concentration in expired gas was expressed as the amount found in 2100 litre of air.

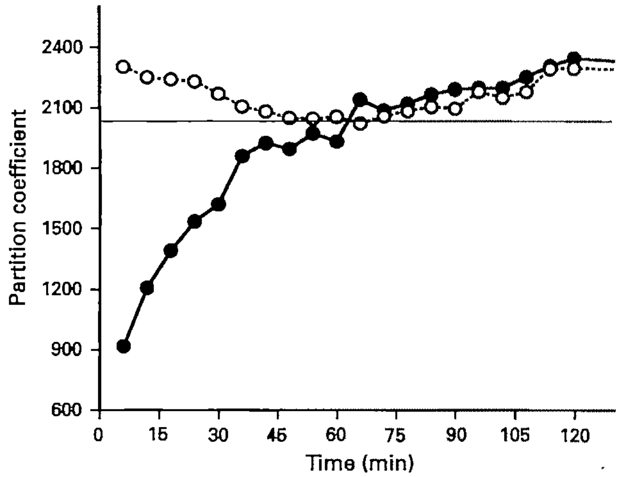


Figure 4 Blood–expired gas partition coefficient of ethanol during isoflurane anaesthesia (○) and in the awake state (●) (mean). Ethanol concentration in expired gas was expressed as the amount found in 2100 litre of air.

state (fig. 1). In venous blood, this difference was 34 % (fig. 1). The agreement between expired air and blood samples was stronger during general anaesthesia than in the awake state (fig. 2).

The expired gas–venous differences in ethanol concentration were close to zero during infusions of ethanol in anaesthetized patients, while they were markedly positive when the patients were awake (AUC, $P < 0.05$). After infusion, these differences were reduced and remained slightly negative during the pseudolinear phase of ethanol elimination (fig. 3).

These relationships represented a blood–expired gas partition coefficient for ethanol of 2238 (356) during infusion of ethanol in anaesthetized patients, while it was only 1339 (411) when the patients were awake. After infusion, these coefficients were 2107 (275) and 2118 (257), respectively (fig. 4).

The pharmacokinetic rate constants describing the distribution and elimination of ethanol showed similar values, regardless of whether or not the subjects were anaesthetized (table 1). However, V_c for ethanol in blood was only half as large during general anaesthesia (Wilcoxon's test, $P < 0.03$).

Body temperature was lower in anaesthetized compared with awake patients. The difference increased gradually from 0.5 °C and 1.5 °C but was significant at all times (table 2).

Discussion

We have found that breath sampling during isoflurane anaesthesia reflected the alcohol load well and with the same precision as in the conscious state. The slightly higher mean ethanol concentration obtained during anaesthesia must be considered in view of the markedly increased ethanol concentration in blood that returned to the lungs. This increase can be attributed to the reduction in central distribution volume (V_c) for ethanol. That a reduction in V_c could be detected in venous blood but not in expired gas indicates that it occurred after the blood had passed the pulmonary circulation, namely at the capillary level in peripheral tissues.

The distribution of ethanol to and from the tissues implies that the expired gas–venous difference in concentration is positive during ethanol infusion and becomes negative when mixing is complete throughout the total body water [14, 15]. This pattern was seen when our patients were awake, but the positive difference observed during infusion was absent when they were anaesthetized. The negligible expired gas–blood difference is consistent with vaso-

Table 1 Pharmacokinetic variables of ethanol (mean (SD)) derived by curve fitting concentration–time data obtained from analysis of ethanol concentration in expired gas ($\times 2100$) and venous blood. A = Theoretical concentration of ethanol when distribution phase is extrapolated to time = 0. α = first-order exponential distribution rate constant. B = theoretical concentration of ethanol when elimination phase is extrapolated to time = 0. β = zero-order elimination rate constant

	General anaesthesia		Awake	
	Expired gas	Blood	Expired gas	Blood
A (g litre^{-1})	1.48 (0.61)	2.33 (0.67)	1.26 (0.32)	0.55 (0.21)
α (min^{-1})	0.13 (0.05)	0.14 (0.05)	0.13 (0.04)	0.11 (0.03)
$T_{\frac{1}{2}}^{\alpha}$ (min)	6.4 (3.0)	5.5 (2.4)	5.8 (1.9)	6.9 (1.8)
B (g litre^{-1})	0.85 (0.13)	0.86 (0.11)	0.76 (0.06)	0.78 (0.08)
β (10^{-3} g litre^{-1} min^{-1})	3.81 (1.01)	4.21 (1.20)	3.63 (0.98)	3.14 (1.20)
V_c (litre)	12.0 (2.5)	8.6 (0.9)	13.6 (2.8)	20.9 (5.3)
V^{extrap} (litre)	32.1 (3.6)	31.6 (4.7)	35.3 (6.2)	34.6 (6.0)
AUC (g litre^{-1} min)	66.0 (14.4)	75.0 (16.6)	58.4 (9.9)	55.8 (15.5)

Table 2 Body temperature (°C) during the experiments with ethanol infusions (mean (SD)). *Measured after anaesthesia had been induced

Time (min)	General anaesthesia	Awake
0	36.4 (0.5)*	37.0 (0.4)
30	36.0 (0.3)	37.0 (0.4)
60	35.8 (0.4)	37.1 (0.3)
90	35.6 (0.4)	37.0 (0.4)
120	35.5 (0.5)	37.0 (0.4)

dilatation, which decreases the transit time for blood in the tissues and results in less complete mixing of ethanol between the blood and interstitial fluid [16]. (The even slightly negative expired gas–venous difference can be explained by an expired gas–arterial difference averaging -0.06 g litre^{-1} during rapid infusion of ethanol [15].) Vasodilatation "arterializes" venous samples and also makes the concentrations in expired gas and venous blood more similar. Recent experiments in which local vasodilatation was induced by warming the site used for blood sampling confirmed that such treatment reduces V_c for ethanol [15].

The rationale for measuring ethanol in expired gas is based on the assumption of a fairly stable equilibrium between ethanol concentration in the capillary blood of the lungs and alveolar air. The agreement between the blood and expired gas data is usually reported after multiplying the expired gas concentration with the blood–expired gas partition coefficient. However, this coefficient tells us that the ethanol concentration is always about 2100 times higher in blood than in expired gas. Therefore, reabsorption of ethanol from the gas mixture in the breathing system is only a theoretical source of ethanol administration in anaesthetized patients.

Preliminary experiments showed that the heat and moisture exchanger and soda lime together absorbed about 30% of the ethanol in the breathing system. This suggests that sampling should be performed close to the tracheal tube for accurate analysis of end-expiratory ethanol concentration [6] and that the results are probably unaffected by ethanol in inspired gas. The confounding effect of using an extremely small fresh gas flow was challenged further by turning it off completely for 30 s before each breath sampling. However, our results imply no bias in the breath analysis from this practice. During both experiments, the blood–expired gas partition coefficient for ethanol during the pseudolinear phase of ethanol metabolism was 2113, on average, which was similar to that found in previous studies [6–8, 12]. On the other hand, this coefficient was markedly lower during infusion of ethanol in awake patients [14] which suggests that a close correlation between expired gas and venous blood samples during rapid absorption of irrigating fluid marked with ethanol cannot be expected. In fact, the agreement between expired gas and blood was closer during anaesthesia.

The present study suggests that anaesthesia-induced vasodilatation is the main confounder when measuring fluid absorption by ethanol monitoring during surgery. This view implies that the effects of atelectasis, tracheal intubation and moderate hypothermia on breath alcohol analyses are very small or cancel out. In particular, the lower body temperature in the anaesthetized patients would be expected to increase the blood–expired gas partition coefficient of ethanol by almost 10% during the pseudolinear phase of ethanol metabolism [7, 8]. However, this coefficient was almost identical in the groups at that time.

The pharmacokinetic model we used allows separate evaluation of the distribution and the elimination parts of the blood-ethanol concentration profile. A previous study showed that the half-time for distribution of ethanol into the total body water ($T_{\frac{1}{2}}^{\alpha}$) averaged 6.6 min after i.v. infusion of ethanol at different rates in young men and women [10]. In our present report, $T_{\frac{1}{2}}^{\alpha}$ was 6.9 min in venous blood when the female subjects were awake. In the anaesthetized state, we expected that the higher venous return of ethanol would correspond to a prolonged $T_{\frac{1}{2}}^{\alpha}$. Instead, it tended to be shorter. This result, and the fact that equilibration of ethanol requires as long as 30 min to become complete, supports the assumption that α represents equilibration between well perfused and poorly perfused anatomical regions of the body rather than across the cellular membranes [15].

Acknowledgement

We are indebted to Dr Ulf Jansson and his staff at the Department of Clinical Chemistry, Sundsvall Central Hospital, for analysing our plasma ethanol samples.

References

1. Hahn RG. Early detection of the TUR syndrome by marking the irrigating fluid with 1% ethanol. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 146–151.
2. Hahn RG. Prevention of the TUR syndrome by detection of trace ethanol in the expired breath. *Anaesthesia* 1990; **45**: 577–581.
3. Duffy S, Cruise M, Reilly C, Reid PC, Sharp F. Ethanol labeling; detection of early fluid absorption in endometrial resection. *Obstetrics and Gynecology* 1992; **79**: 300–303.
4. Olsson J, Hahn RG. Ethanol monitoring of irrigating fluid absorption in transcervical resection of the endometrium *Acta Anaesthesiologica Scandinavica* 1995; **39**: 252–258.
5. Hultén J, Sarma VJ, Hjertberg H, Palmquist B. Monitoring of irrigating fluid absorption during transurethral prostatectomy. *Anaesthesia* 1991; **46**: 349–353.
6. Stalberg HP, Hahn RG, Jones AW. Ethanol monitoring of transurethral prostatic resection during inhalation anesthesia. *Anesthesia and Analgesia* 1992; **75**: 983–988.
7. Jones AW. Role of rebreathing in determination of blood–breath ratio of expired ethanol. *Journal of Applied Physiology* 1983; **55**: 1237–1241.
8. Jones AW. Determination of liquid–/air partition coefficients for dilute solutions of ethanol in water, whole blood, and plasma. *Journal of Analytical Toxicology* 1983; **7**: 193–197.
9. Jones AW, Hahn RG, Stalberg HP. Distribution of ethanol and water between plasma and whole blood; inter- and intra-individual variations after administration of ethanol by intravenous infusion. *Scandinavian Journal of Clinical and Laboratory Investigation* 1990; **50**: 775–780.
10. Hahn RG, Norberg Å, Jones AW. Rate of distribution of ethanol into the total body water. *American Journal of Therapeutics* 1995; **2**: 50–56.
11. Wagner JG. Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. *Journal of Pharmacokinetics and Biopharmaceutics* 1976; **4**: 443–467.
12. Holford NHG. Clinical pharmacokinetics of ethanol. *Clinical Pharmacokinetics* 1987; **13**: 273–292.
13. Hull CJ. *Pharmacokinetics for Anaesthesia.* Oxford: Butterworth-Heinemann Ltd, 1991; 170–186.
14. Hahn RG, Jones AW, Billing B, Stalberg HP. Expired-breath ethanol measurement in chronic obstructive pulmonary disease: implications for transurethral surgery. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 393–397.
15. Norberg Å, Jones AW, Hahn RG. Pharmacokinetics of ethanol in arterial and venous blood and in end-expired-breath during vasconstriction and vasodilatation. *American Journal of Therapeutics*, 1995; **2** (12): (in press).
16. Sonnenberg GE, Keller U. Sampling of arterialized heated-hand venous blood as a non-invasive technique for the study of ketone body kinetics in man. *Metabolism* 1982; **31**: 1–54.

British Journal of Anaesthesia 1996; **76**: 90–98

Perioperative mucosal pH and splanchnic endotoxin concentration in orthotopic liver transplantation[†]

M. Welte, B. Pichler, J. Groh, M. Anthuber, K.-W. Jauch, E. Pratschke,
F.-P. Lenhart, M. Haller, L. Frey and K. Peter

Summary

Although impairment of splanchnic perfusion may induce mucosal hypoxia and endotoxaemia during orthotopic liver transplantation (OLT), little is known about the changes in mucosal oxygenation during and after the procedure. To study the effects of liver surgery itself on mucosal pH (pH_i) and the response of pH_i to acute changes in portal flow, we measured gastric pH_i during six liver resections using tonometry: in two patients, after clamping of the hepatoduodenal ligament, pH_i decreased within 30 min and recovered promptly after reperfusion. We then investigated gastric and sigmoid pH_i (pH_{ig}, pH_{is}) during the perioperative phase in 18 OLT. Median pH_i values were low before surgery (pH_{ig} 7.28 (first/third quartiles 7.22/7.34); pH_{is} 7.27 (7.12/7.36)). Although global oxygen delivery and haemodynamic variables remained constant and veno-venous bypass (VVB) was used to maintain portal flow, pH_i declined during the anhepatic phase (pH_{ig} 7.19 (7.13/7.23), $P < 0.01$; pH_{is} 7.13 (7.06/7.24), $P < 0.05$). After reperfusion of the graft, pH_i recovered and did not differ from baseline values by the end of OLT. After operation pH_{ig} increased further, reaching the highest values 30 h after ICU admission (7.34 (7.26/7.38)). In the intraoperative period, no significant endotoxaemia was observed either in portal or systemic blood. The maximum reduction in pH_i was related neither to the duration of VVB and OLT nor to the number of red cell units transfused. pH_i after reperfusion did not correlate with graft viability or dysfunction of the lung or kidney. We conclude that pH_i indicates mucosal ischaemia during OLT which is not necessarily associated with endotoxaemia, and intraoperative pH_i monitoring does not appear to be a valuable predictor of postoperative graft failure and organ dysfunction. (*Br. J. Anaesth.* 1996; **76**: 90–98)

Key words

Liver, transplantation. Gastrointestinal tract, pH. Monitoring, pH oesophageal.

Perioperative changes in haemodynamic and metabolic variables and in tissue oxygenation are well established during orthotopic liver transplantation (OLT) [1, 2]. However, little is known about regional perfusion and oxygenation, particularly of the splanchnic organs, although intestinal hypoxia may be a source of postoperative morbidity and graft dysfunction [3–5]. In patients with liver failure secondary to cirrhosis and presenting with a hyperdynamic circulatory state, impaired tissue oxygenation has been observed during operation, although global oxygen delivery and perfusion pressure were adequately maintained [2]. It may be postulated that inadequate tissue oxygenation occurs during transplantation in the intestinal mucosa, which is highly susceptible to a reduction in blood flow. This might be most relevant during the anhepatic phase, when clamping of the portal vein is required for the recipient hepatectomy. Impaired intestinal perfusion may induce mucosal barrier dysfunction and translocation of bacteria and endotoxin into the systemic and lymph circulations [4, 6, 7].

Endotoxaemia has been reported to occur during OLT. The highest endotoxin concentrations were measured at the end of the anhepatic phase before reperfusion of the graft, and endotoxaemia was found to correlate with postoperative patient outcome [8, 9]. To avoid the deleterious effects of portal clamping on intestinal perfusion and to limit the progression of tissue hypoxia, veno-venous bypass (VVB), which drains blood from the portal to the superior caval vein, has been suggested [2, 10]. Mucosal oxygenation, however, has not been assessed adequately during liver transplantation. It is not known if mucosal ischaemia occurs during OLT, if it is associated with endotoxaemia or if the use of VVB preserves mucosal oxygenation.

To assess mucosal oxygenation, we measured gastrointestinal mucosal pH (pH_i) using tonometry [11]. In experimental studies pH_i was found to be a sensitive marker of impaired intestinal blood flow [12–14] and adequacy of mucosal oxygen delivery [15]. In clinical trials a low pH_i has been shown to be

---

M. Welte*, MD, B. Pichler, MD, J. Groh, MD, F.-P. Lenhart, MD, M. Haller, MD, L. Frey, MD, K. Peter, MD (Institute of Anaesthesiology); M. Anthuber, MD, K.-W. Jauch, MD, E. Pratschke, MD (Department of Surgery); Ludwig-Maximilians-University Munich, Klinikum Grosshadern, Munich, Germany. Accepted for publication: July 30, 1995.

*Address for correspondence: Institut für Anaesthesiologie, Ludwig-Maximilians-Universität München, Klinikum Grosshadern, Marchioninistr. 15, 81366 Munich, Germany.

[†] Presented in part at the Annual Meeting of the American Society of Anaesthesiologists, San Francisco, CA, USA, October 15–19, 1994.

an indicator of intestinal ischaemia after aortic surgery [16] and cardiopulmonary bypass [17], and a prognostic factor in critically ill patients [18, 19]. More recently, *gastric* pH_i measured 30 min after graft reperfusion has been reported to be an independent indicator of early graft viability in OLT [5].

The purpose of this study was to assess gastric and sigmoid mucosal pH during the perioperative phase of OLT. We hypothesized that preservation of splanchnic blood flow using VVB would prevent a reduction in pH_i during the anhepatic phase, a low pH_i would be related to the occurrence of endotoxaemia and low pH_i values persisting after graft reperfusion would be an indicator of poor graft function.

Because at the time this study was performed VVB was used routinely for haemodynamic support during OLT in our institution, we could not include a control group without VVB. To assess the ability of pH_i to detect acute intraoperative changes of mucosal perfusion in humans and to determine the effects of laparotomy and hepatic surgery on mucosal oxygenation, we measured gastric pH_i in six patients undergoing hepatic resection before the study in OLT patients. However, it was not our intention to compare the results obtained in liver resection patients with those obtained in the different patient populations undergoing OLT.

Patients and methods

After obtaining approval from the local Ethics Committee and informed consent, we studied six patients undergoing liver resection and 18 consecutive OLT in 16 adult patients. Patient characteristics and indications for hepatic resection or transplantation are summarized in tables 1 and 2.

One hour before surgery flunitrazepam 1–2 mg orally was given for premedication. Anaesthesia was induced with either thiopentone 3–5 mg kg^{-1} or etomidate 0.1–0.3 mg kg^{-1}, fentanyl 3–7 µg kg^{-1} and pancuronium 0.1 mg kg^{-1}, and maintained with 0.4–1.0 vol% isoflurane, a continuous infusion of fentanyl 3.5–7.0 µg kg^{-1} h^{-1} and incremental doses of pancuronium. The trachea was intubated and the lungs ventilated throughout OLT with 50% oxygen in air. Tidal volume and ventilatory frequency were adjusted to maintain Pa_{CO_2} at 4.8–5.3 kPa.

Standard monitoring included a 20-gauge radial artery catheter, a 12-French gauge triple-lumen central venous catheter and a 7-French gauge triple-lumen thermodilution fibreoptic pulmonary artery catheter (Abbott Critical Care, Mountain View, CA, USA). For perioperative antiobiotic prophylaxis, imipenem 0.5–1 g was given before operation. Selective digestive decontamination (SDD) was started 1 h before operation and repeated every 6 h by oral administration of polymyxin 50 mg, gentamicin 80 mg, vancomycin 125 mg and amphotericin B 5 ml [20]. Five patients had received systemic antibiotics for several days before operation. Gastric acid secretion was blocked before induction of anaesthesia with omeprazole 40 mg i.v. [21].

After induction of anaesthesia, tonometry catheters (Tonomomitor, Tonometrics, Worcester, MA, USA) were positioned in the stomach and the sigmoid colon. The correct position of the balloon was confirmed by intraoperative palpation. The colon had been emptied before operation by enema. The gastric catheter was left in place until the second postoperative day while the sigmoid catheter was removed at the end of surgery to avoid anal pressure necrosis.

The surgical procedure was standardized and all transplantations were performed by the same two surgeons (K.-W.J., E.P.) Orthotopic transplantation was performed in all patients. After percutaneous insertion of jugular (15- or 17-French gauge) and femoral (17-French gauge) cannulae and cannulation of the portal vein (24-French gauge wire-reinforced cannula) a heparin coated porto–femoro–jugular bypass (centrifugal pump, Biomedicus Medtronic, MN, USA) was used during the anhepatic phase. Bypass flow was adjusted initially to maximal values by increasing the pump speed near to the level where the portal or femoral vein collapsed. Flow rates ranged between 30 and 50% of actually measured cardiac output.

Red blood cells (RBC) were transfused to maintain packed cell volume (PCV) above 25%. Fresh frozen plasma (FFP) was substituted to increase partial thrombin time to 50% of normal reference values. Platelet concentrates were given when the platelet count was less than 30×10^9 $litre^{-1}$, depending on platelet function, determined from *ex vivo* bleeding time and volume [22].

Haemodynamic measurements were made, including: heart rate (HR), mean arterial pressure (MAP), mean pulmonary arterial pressure (PAP), central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP). Cardiac output (CO) was obtained from triplicate thermodilution measurements varying by less than 10%, performed randomly throughout the respiratory cycle. Core body temperature was recorded from the thermistor of the pulmonary artery catheter.

Central venous blood samples were obtained for serial analyses of haemoglobin, PCV, platelet count, coagulation profile (PT, aPTT, antithrombin III, fibrinogen), electrolyte (sodium, potassium, ionized calcium) and glucose concentrations. In addition, alanine–leucine transferase (ALT; optical standard method of DGKC, Boehringer Mannheim, Germany), coagulation factor V (optical method, CA 5000) and creatinine clearance (serum creatinine, Jaffe method, Boehringer Mannheim, Germany) were determined after operation. Arterial and pulmonary arterial blood samples were obtained for blood-gas analyses and measurement of oxygen saturation (ABL 520 Radiometer, Copenhagen, Denmark). Global oxygen delivery (Do_2) and consumption indices ($\dot{V}o_2$) in addition to oxygen extraction ratio were calculated from arterial and mixed venous oxygen contents and thermodilution derived CO. For measurement of plasma lactate concentration, blood samples from the pulmonary artery and portal vein were stored immediately on ice, centrifuged and analysed within 15 min (Kodak Ektachem Clinical Chemistry slide for lactate).

Plasma endotoxin concentration was measured using the limulus amoebocyte lysate test (Coatest Endotoxin, Chromogenix, Mölndal, Sweden). Blood samples from a separate lumen of the central venous catheter, the portal vein and the portal bypass catheter (during VVB) were obtained in pyrogen-free disposable syringes, anticoagulated with heparin, centrifuged immediately on ice for 5 min at 1200 rpm, and stored at −80 °C for later analysis. Standards were obtained from *E. coli* endotoxin (0111:B4 standard endotoxin) in sterile water. The sensitivity of the test in our laboratory is 1.0 pg ml^{-1}.

Gastric and sigmoid tonometer balloons were filled with 5 ml of room temperature normal saline. For measurement of pH_i, the first 1 ml of saline aspirated from the balloon was discarded (dead-space), and the remaining fluid was collected and immediately analysed for $P\text{CO}_2$ ($P\text{CO}_2$tono; ABL 520, Radiometer, Copenhagen, Denmark). Immediately after each collection, the tonometer was refilled. Simultaneously, an arterial blood-gas sample was obtained. Blood-gas analysis was performed at 37 °C without correction for temperature. pH_i was calculated from arterial HCO_3^- and $P\text{CO}_2$tono using a modified Henderson–Hasselbalch equation [11]. Because equilibration of carbon dioxide between saline in the balloon and mucosa is time and temperature dependent, $P\text{CO}_2$tono was corrected for dwell time and core temperature by multiplying the measured value by a correction factor (Tonometrics product insert 002-TGS) [16]. To avoid over extrapolation, the dwell time was extended as long as possible between consecutive intraoperative measurements (mean 48 (SD 21) min).

Intraoperative measurements were performed before bypass (I), 30 min after the start of VVB (II), 5 min before reperfusion of the graft (III), 30 min into the neohepatic phase (IV) and at the end of surgery when the peritoneum was closed (V). After operation, haemodynamic and oxygenation variables and gastric pH_i were assessed 6 h after admission to the intensive care unit (ICU; VI) and 12 (VII) and 24 h (VIII) later.

Before the study in OLT patients, we measured gastric pH_i in six patients undergoing liver resection (table 1). The perioperative regimen was the same as in the OLT patients except that SDD was not administered. The same haemodynamic, oxygenation and laboratory variables were assessed except for sigmoid pH_i and endotoxin concentration. In two patients the hepatic artery and portal vein were clamped for 41 and 63 min, respectively, to reduce bleeding from the hepatic resection surface.

Measurements were obtained after induction of anaesthesia, before surgery, 30 min after skin incision, during liver resection and at skin closure. In patients with clamping of the hepatoduodenal ligament, additional measurements were performed during clamping.

STATISTICAL ANALYSIS

The Kolmogorov–Smirnov test revealed non-normal distribution of data; therefore, non-parametric tests were used. Friedman's test was performed to examine the effect of time (SPSS for Windows, SPSS Software, Munich, Germany). For significant *F* values the following measurements were compared by Wilcoxon signed ranks test: before VVB (I) *vs* VVB (III), before bypass (I) *vs* end of surgery (V), and before bypass (I) *vs* 24 h after ICU admission (VIII). Bonferroni correction was applied as appropriate and differences were considered significant if $P < 0.05$. Bivariate correlations between pH_i and blood-gas variables and between pH_i and duration of VVB, duration of surgery and blood loss were determined by Spearman's rank correlation test. Data are reported as median (first/third quartiles).

Results

Patient data, indications for surgery and transfusion requirements of patients undergoing hepatic resection are presented in table 1.

Haemodynamic and oxygenation variables remained unchanged throughout surgery (data not shown). Although pH_i decreased slightly in all patients after laparotomy, no significant overall effects of time were observed for arterial pH and gastric pH_i (Friedman test: $P = 0.22$ for arterial pH, $P = 0.1$ for pH_i) (fig. 1). In the two patients, in whom portal blood flow was interrupted transiently by clamping of the hepatoduodenal ligament, pH_i decreased instantaneously. The lowest pH_i value (6.95) was encountered in the patient with the longest clamping time (63 min). After release of the portal clamp, pH_i returned to the range of baseline values and did not differ from pH_i in patients without portal clamping by the end of surgery.

Patient data, indications for transplantation, duration of surgery and VVB, respectively, units of RBC and FFP transfused, and duration of postoperative ventilatory support and ICU stay in OLT patients are summarized in table 2. Cirrhosis was the most common indication for transplantation (13 of 16 patients). In two patients, re-transplantation was performed 4 and 51 days after the first transplantation for primary graft non-function and

Table 1 Patient characteristics, indications, duration of surgery, ventilatory support and ICU stay, and blood product requirements of patients undergoing liver resection (median (Q1/Q3)). RBC = red blood cells; FFP = fresh frozen plasma

	Liver resection ($n = 6$)
Age (yr)	60.0 (53.4/74.3)
Weight (kg)	66.5 (56.6/78.80)
Sex (F/M)	2/4
Indications	
hepatocellular carcinoma	6
Duration of surgery (min)	198 (128/250)
Blood product requirements	
RBC (total units)	0
FFP (total units)	0
Duration of ventilatory support (days)	0
Duration of ICU stay (days)	0

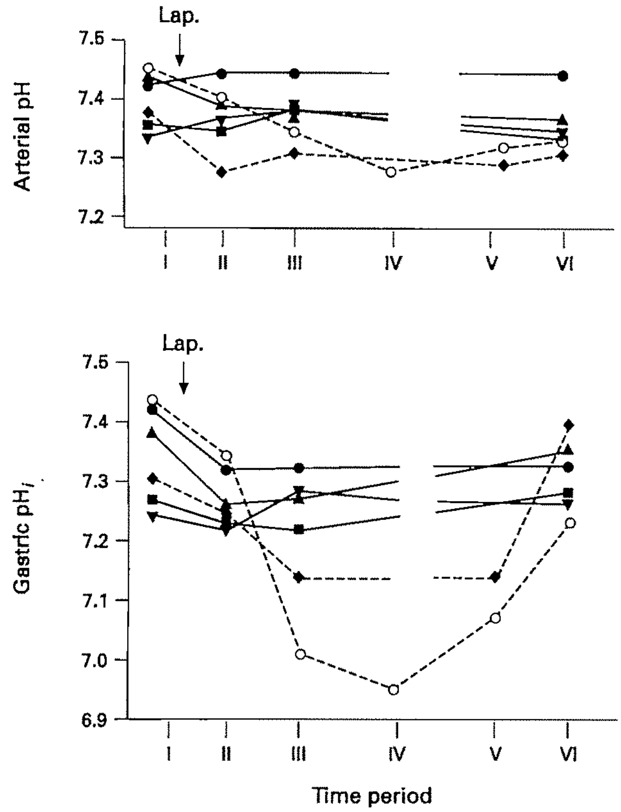


Figure 1 Arterial pH and gastric pH$_i$ in six patients undergoing liver resection. In two patients the hepatoduodenal ligament was transiently clamped (broken lines). I = before skin incision; II = after laparotomy (Lap.); III = during hepatic resection; IV = after 60 min clamping of the hepatoduodenal ligament (one patient); V = 30 min after declamping of the hepatoduodenal ligament (two patients); and VI = after closure of the peritoneum.

Table 2 Patient data, indications, duration of surgery, veno-venous bypass (VVB), ventilatory support and ICU stay, and blood product requirements in patients undergoing orthotopic liver transplantation (OLT) (median (Q1/Q3)). Stage I = Pre-anhepatic phase; stage II = anhepatic phase; stage III = neo-hepatic phase. RBC = red blood cells; FFP = fresh frozen plasma

	OLT ($n = 16$; 18 OLT)
Age (yr)	49.5 (40.8/55.3)
Weight (kg)	70.0 (59.5/78.0)
Sex (F/M)	4/12
Indications	
cirrhosis	
Post-hepatitic	8
Alcoholic	3
hepatocellular carcinoma	2
Budd–Chiari syndrome	1
Primary biliary cirrhosis	2
Re-OLT	
Chronic rejection	1
Primary non-function	1
Duration of surgery (min)	295 (248/380)
Duration of VVB (min)	110 (87/132)
Blood product requirements	
RBC (total units)	11 (7/17)
Stage I	1.5 (0/3.3)
Stage II	5 (3.0/7.3)
Stage III	4.0 (3.0/8.3)
ICU	3.5 (0.8/9.5)
FFP (total units)	22 (13/43)
Stage I	3.5 (0/10.3)
Stage II	12.0 (5.0/16.5)
Stage III	9 (3.8/18.8)
ICU	5 (1.5/15.8)
Duration of ventilatory support (days)	2.5 (1.6/6.3)
Duration of ICU stay (days)	8 (7/18)

chronic rejection, respectively. RBC and FFP requirements were highest during the anhepatic phase.

Central haemodynamic variables and Do_2 index were essentially unchanged throughout the peri-operative period (table 3). MAP declined slightly during the anhepatic and neohepatic phases and was significantly lower at the end compared with the beginning of surgery ($P < 0.01$). CI remained high, which is typical for patients presenting with cirrhosis. $\dot{V}o_2$ index changed significantly over time (Friedman test: $P = 0.02$); $\dot{V}o_2$ index was low during OLT and increased after admission to the ICU (table 3).

The perioperative course of mixed venous lactate concentration, mixed venous oxygen saturation ($S\bar{v}_{O_2}$), arterial pH, gastric and sigmoid pH$_i$, and endotoxin concentrations in mixed venous and portal blood is shown in figure 2. Mixed venous lactate concentration increased continuously during transplantation, peaked after graft reperfusion (5.9 (3.5/7.15) mmol litre^{-1}; $P < 0.01$ *vs* baseline) and declined to baseline values 30 h after ICU admission. $S\bar{v}_{O_2}$ remained constant at a high level (> 87%) during OLT, began to decline after operation and reached its lowest value 30 h after ICU admission (76 (70/79)%; $P < 0.01$ *vs* baseline). Arterial pH decreased significantly from 7.39 (7.35/7.43) at the beginning of OLT to 7.32 (7.24/7.34) during VVB ($P < 0.01$). To prevent further progression of metabolic acidosis, sodium bicarbonate (110 mmol) was given to 12 patients during the anhepatic or neohepatic phase. After reperfusion of the graft, arterial pH remained less than baseline values and recovered to normal values after ICU admission.

Gastric pH$_i$ (pH$_{ig}$) decreased significantly from baseline values of 7.28 (7.22/7.34) to 7.19 (7.13/7.23) during VVB ($P < 0.01$) and remained low during the anhepatic phase. After reperfusion of the graft, pH$_i$ increased within 30 min and did not differ from baseline values at the end of OLT (ns). After operation, gastric pH$_i$ increased further, reaching the highest values 18 and 30 h after ICU admission (7.34 (7.28/7.38) and 7.34 (7.26/7.38), respectively). After adjusting for multiple comparisons, the difference in gastric pH$_i$ between baseline and 30 h ICU did,

Table 3 Perioperative changes in haemodynamic and oxygenation variables (median (Q1/Q3)). MAP = Mean arterial pressure; PAP = mean pulmonary arterial pressure; PCWP = pulmonary artery wedge pressure; CI = cardiac index; Hb = haemoglobin concentration; Ca_{O_2} = arterial oxygen content; $C\bar{v}_{O_2}$ = mixed venous oxygen content; Do_2 index = global oxygen delivery index; $\dot{V}o_2$ index = oxygen consumption index. I = Before veno-venous bypass, II = 30 min of veno-venous bypass, III = 5 min before reperfusion, IV = 30 min of neohepatic phase, V = end of surgery, VI = ICU admission, VII = 12 h in ICU, VIII = 24 h in ICU. $^{**}P < 0.01$: beginning *vs* end of surgery

	Intraoperative					ICU		
	I	II	III	IV	V	VI	VII	VIII
MAP (mm Hg)	84	82	74	68	68**	84	95	94
	(78/92)	(68/85)	(65/86)	(61/80)	(63/78)	(72/95)	(90/103)	(81/103)
PAP (mm Hg)	19	19	21	22	22	19	21	21
	(15/28)	(13/27)	(15/27)	(15/26)	(13/26)	(15/29)	(19/29)	(16/27)
PCWP (mm Hg)	12.0	8.0	10.0	11.0	8.5	13.0	13.5	10.0
	(8.5/15.0)	(6.0/13.3)	(8.0/15.8)	(8.0/17.0)	(6.0/16.3)	(9.3/14.0)	(10.0/15.8)	(7.5/16.0)
CI (litre min^{-1} m^{-2})	5.11	4.39	4.64	5.60	5.06	5.10	5.40	4.76
	(3.64/6.43)	(3.58/5.43)	(3.59/5.43)	(4.67/7.01)	(4.31/6.56)	(3.67/6.19)	(4.57/6.27)	(3.32/6.05)
Hb (g dl^{-1})	10.2	8.3	9.6	8.5	9.3	9.4	9.6	9.0
	(8.3/11.2)	(7.6/9.6)	(8.4/10.9)	(7.7/10.0)	(9.1/10.8)	(8.5/10.3)	(8.6/10.3)	(8.6/10.3)
Ca_{O_2} (ml/100 ml blood)	12.7	11.9	13.4	11.5	12.8	12.4	12.5	12.4
	(11.7/14.7)	(10.4/14.0)	(11.9/14.4)	(10.8/12.9)	(11.7/14.3)	(11.2/14.2)	(11.3/13.5)	(11.7/12.8)
$C\bar{v}_{O_2}$ (ml/100 ml blood)	10.4	10.1	10.7	10.3	11.1	10.4	10.2	9.6
	(9.0/12.9)	(9.1/11.8)	(9.8/14.5)	(8.7/10.8)	(9.3/12.8)	(9.7/11.6)	(9.6/11.5)	(8.5/9.9)
Do_2 index (ml min^{-1} m^{-2})	639	519	633	684	687	694	677	699
	(502/807)	(446/802)	(455/774)	(525/865)	(627/760)	(551/794)	(391/756)	(522/716)
$\dot{V}o_2$ index (ml min^{-1} m^{-2})	96	76	59	85	90	165	151	143
	(48/111)	(53/113)	(47/120)	(64/130)	(57/112)	(141/188)	(111/198)	(118/222)
O_2 extraction ratio (%)	16.7	13.1	9.1	14.5	13.0	20.5	21.5	25.0
	(6.5/22.4)	(6.7/23.1)	(6.6/24.4)	(10.3/18.2)	(8.0/18.2)	(16.5/30.9)	(18.3/27.3)	(19.2/32.7)

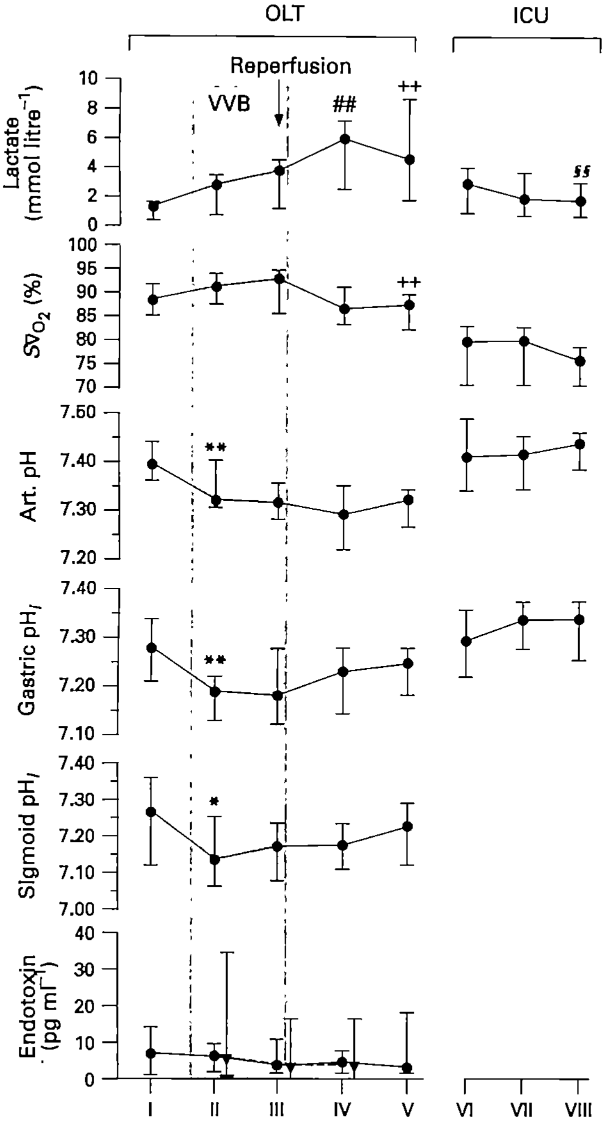


Figure 2 Arterial lactate concentration, mixed venous oxygen saturation ($S\bar{v}_{O_2}$), arterial pH, gastric pH_i, sigmoid pH_i and mixed venous (●) and portal (▲) endotoxin concentration. The duration of veno-venous bypass (VVB) is represented by the shaded area. I = before VVB; II = 30 min of VVB; III = 5 min before graft reperfusion; IV = 30 min after graft reperfusion; V = end of OLT; VI, VII, VIII = 6, 18 and 30 h after ICU admission, respectively. $^*P < 0.05$, $^{**}P < 0.01$: before VVB *vs* 30 min of VVB; $^{\#\#}P < 0.01$: 30 min of VVB *vs* 30 min of graft reperfusion; $^{\dagger\dagger}P < 0.01$: before VVB *vs* end of OLT; $^{\S\S}P < 0.01$: before VVB *vs* 30 h in ICU.

however, not reach statistical significance ($P = 0.1$). The intraoperative course of sigmoid pH_i (pH_{is}) showed essentially the same pattern as gastric pH_i; the lowest values were measured during VVB (7.13, 7.06/7.24), and sigmoid pH_i at the end of surgery did not differ significantly from baseline.

The maximal intraoperative decrease in gastric or sigmoid pH_i did not correlate either with the duration of VVB (pH_{ig}, $r = 0.17$; pH_{is}, $r = 0.34$; ns) or with the number of RBC units transfused (pH_{ig}, $r = -0.19$; pH_{is}, $r = 0.04$; ns). pH_i values obtained after graft reperfusion did not correlate with duration of postoperative ventilatory support (pH_{ig}, $r = 0.41$; pH_{is}, $r = 0.29$; ns) (table 2), duration of ICU stay (pH_{ig}, $r = 0.39$; pH_{is}, $r = 0.29$; ns) (table 2) or with creatinine clearance on the second postoperative day (pH_{ig}, $r = 0.34$; pH_{ig}, $r = -0.18$; ns) (table 4).

Table 4 Postoperative tests of hepatocellular integrity, hepatic function and renal function (median (Q1/Q3)). ALT = Alanine–leucine transferase; factor V = activity of coagulation factor V as a percentage of reference values of normal population; prothrombin time as a percentage of reference values of normal population; creatinine clearance as a percentage of reference values of normal population normalized for body surface area

	ICU	
	VI	VIII
ALT (U/L)	216 (96/397)	251 (109/676)
Factor V (%)	42 (18/68)	52 (9/77)
Prothrombin time (%)	52 (44/62)	48 (41/58)
Creatinine clearance (%)	—	71 (39/98)

Postoperative hepatic function, as assessed by plasma activity of factor V and prothrombin time (table 4), and the degree of hepatocellular damage, as assessed by serum ALT (table 4), did not correlate with pH_i after reperfusion of the graft (pH_{ig}, $r = 0.28$; pH_{is}, $r = 0.34$; ns) or at the end of surgery (pH_{ig}, $r = 0.31$; pH_{is}, $r = -0.15$; ns). In the one patient requiring re-transplantation for primary graft non-function, pH_i values after graft reperfusion (pH_{ig} 7.28, pH_{is} 7.23) and at the end of OLT (pH_{ig} 7.27, pH_{is} 7.28) were in the range obtained from patients with adequate primary graft function.

Plasma endotoxin concentrations were determined during the course of 12 OLT. Endotoxin concentrations in plasma from mixed venous or portal venous blood did not increase significantly during OLT (fig. 2). Correlation analysis revealed no statistically significant relationship between either portal or mixed venous endotoxin concentrations and the lowest values of gastric or sigmoid pH_i measured during the surgical procedure ($r = 0.45$, $r = 0.41$, respectively). One patient presented with high endotoxin concentrations during the anhepatic phase in both mixed venous (58 pg ml^{-1}) and portal blood (71 pg ml^{-1}); at the corresponding time, pH_i values were 7.09 and 7.14 in the stomach and sigmoid colon, respectively.

Discussion

A decrease in mucosal pH_i is considered to reflect inadequate oxygen delivery to the gut to meet metabolic demands. Accordingly, a close relationship between acute changes in splanchnic perfusion and mucosal pH_i has been demonstrated [13]. In pigs, pH_i measured using tonometry decreased as early as 20 min after partial occlusion of the superior mesenteric artery and returned to baseline values within 60 min after release of the occlusion [13]. Although tonometrically measured pH_i slightly underestimated the pH_i changes measured directly with a pH microelectrode, there was a close correlation between values obtained with both methods and the direction of pH_i changes was always reflected accurately by tonometry [13]. Thus the accuracy and response time of tonometry appears adequate to assess acute intraoperative alterations of intestinal perfusion in humans.

Indeed, our study in a limited number of patients undergoing liver resections confirmed that acute interruption of intestinal blood flow was reflected closely by a decrease in tonometrically measured gastric pH_i. In two of six patients in whom portal blood flow was interrupted intentionally by clamping of the hepatoduodenal ligament, gastric pH_i decreased within 30 min after portal occlusion and, after release of the portal clamp, returned to baseline values towards the end of surgery. In patients without portal clamping, pH_i remained essentially unchanged (fig. 1). An increase in gastric pH_i has also been reported after release of chronic intestinal ischaemia caused by portal thrombosis [23]. In contrast, a recent study on the effects of dopexamine on splanchnic oxygenation in cardiac surgical patients revealed that gastric pH_i did not adequately reflect changes in splanchnic blood flow, as measured by the indocyanine green dilution technique [24]. These apparently conflicting results may be caused by different underlying pathophysiological mechanisms; sudden mechanical interruption of venous outflow induces complete stasis of intestinal microvascular blood flow whereas a pharmacologically induced increase in arterial perfusion may redistribute microvascular flow.

Based on the results obtained during hepatic resection, the reversible reduction in both gastric and sigmoid pH_i during the anhepatic phase of OLT implies that transient intramural hypoxia of the gastrointestinal mucosa had developed. Moreover, pH_i decreased although portal blood flow was maintained by VVB allowing total flow rates of up to 50% of cardiac output. As intraoperative pH_i changes were essentially similar at both locations (stomach and sigmoid colon), the reduction in gastric pH_i also cannot be attributed to alterations in gastric mucosal perfusion as induced by surgical manipulations or falsely low pH_i values caused by reflux of alkaline duodenal fluid [25]. Although there are no data on microvascular mucosal perfusion during liver transplantation, the reduction in pH_i observed during the anhepatic phase suggests that preservation of overall portal blood flow by means of VVB did not achieve adequate distribution of intestinal blood flow. Inappropriate flow distribution has been suggested recently to explain the decrease in gastric pH_i, despite the increase in splanchnic oxygen delivery achieved in postoperative cardiac surgical patients by means of dopexamine [24]. In our study pH_i decreased as early as 30 min after the beginning of the anhepatic phase and this suggests that the short period of complete portal clamping necessary to allow insertion of the VVB cannula into the portal vein may be sufficiently long to induce prolonged impairment of microvascular mucosal perfusion. This is supported by the finding that the degree of mucosal acidosis was not related to the duration of VVB.

The increase in lactate concentration observed in our patients during OLT may be interpreted as an indicator of tissue hypoxia only with caution (fig. 2). Steib and colleagues found in a comparable group of hyperdynamic OLT patients that arterial lactate and $S\bar{v}_{O_2}$, indices of tissue oxygenation conventionally used in critically ill patients, failed to accurately reflect tissue hypoxia, as evidenced by supply dependent oxygen consumption [2]. During OLT, lactic acidosis appears to reflect more the absence of metabolic liver function than tissue hypoxia. Moreover, considerable amounts of lactate are added to circulating blood with each unit of stored blood transfused. In fact, we measured lactate concentrations higher than 30 mmol litre^{-1} in stored red cell concentrates (data not shown).

$D\text{O}_2$ index remained unchanged throughout OLT. Consistent with the results of Steib and colleagues, we observed a tendency towards a decreased $\dot{V}\text{O}_2$ index during the anhepatic phase, a finding attributable to a combination of intraoperative hypothermia (temperature at the end of OLT 33.7 (32.8/36.1) °C) and absence of metabolic liver function [2]. During operation, $S\bar{v}_{O_2}$ remained high, which is typical in cirrhotic patients (> 87%), and tended to increase further during the anhepatic phase (93 (86/95)% before reperfusion). As a consequence, continuous intraoperative $S\bar{v}_{O_2}$ monitoring appears to be an inappropriate method to detect tissue hypoxia in hyperdynamic cirrhotic patients. Although increased lactate and decreased $S\bar{v}_{O_2}$ appear not to be reliable markers of tissue hypoxia in cirrhotic patients undergoing OLT, tissue hypoxia has been suggested to be present during OLT, as evidenced by oxygen supply dependency [2]. The decrease in pH_i in the present study clearly demonstrated that the intestinal mucosa is one site of tissue hypoxia.

We are not aware of "normal values" for gastric or sigmoid pH_i in patients with liver cirrhosis. Baseline values in our patients were, however, low compared with normal values reported in the literature for cardiac surgical patients [23] and those regarded as the lower limit for therapeutic interventions in critically ill patients [18]. Thus chronic mucosal hypoxia may be present in end-stage liver cirrhosis associated with portal hypertension and massive collateral circulation. "Normalization" of gastric pH_i on the second postoperative day may indicate furthermore that elimination of portal hypertension and restoration of normal splanchnic perfusion after liver transplantation allow rapid improvement of mucosal blood flow and oxygenation.

We did not find a correlation between intraoperative gastric or sigmoid pH_i measured after reperfusion of the graft and postoperative graft viability. This is in contrast with the results of a recent study that reported a predictive value for postoperative early graft dysfunction of a gastric pH_i value < 7.32 measured 30 min after graft reperfusion [5]. Although this study included a larger number of patients ($n = 35$), its conclusion was based on only one patient requiring re-transplantation for primary graft non-function. More importantly, gastric pH_i values were consistently higher than arterial pH values, a finding attributable to incomplete equilibration of carbon dioxide between the mucosa and the tonometer [11]. In contrast, pH$_i$ in our study was always lower than arterial pH at the corresponding times. In the one patient requiring early re-transplantation, pH$_i$ values did not differ from those of the other patients with an uneventful postoperative course. Furthermore, we could not demonstrate a relationship between intraoperative pH$_i$ and postoperative function of other organ systems, as postoperative creatinine clearance, duration of ventilatory support and total duration of ICU stay were unrelated to intraoperative pH$_i$. It is noteworthy, however, that Downing and colleagues found an association between intraoperative pH$_i$ values < 7.32 and graft dysfunction, acute renal failure, sepsis and the need for ventilatory support after OLT [26]. Unfortunately, this report does not contain details on patient selection and use of tonometry. Moreover, despite the predictive value of pH$_i$ for postoperative complications, the mortality rate was not different between patients with pH$_i$ values higher than 7.32 or lower than 7.32.

In previous studies, endotoxaemia has been demonstrated during liver transplantation, although venous stasis during the anhepatic phase, which could have accelerated the translocation of endotoxin from the gut into the portal blood [6], was avoided by the use of VVB [8, 9]. Moreover, a high systemic endotoxin concentration was a prognostic factor for primary graft non-function, postoperative pulmonary complications and mortality [8, 9]. In our patients significant endotoxaemia was absent in portal and mixed venous blood, although the reduction in pH$_i$ suggested the presence of intraoperative mucosal hypoxia, a situation promoting translocation of enteric micro-organisms (fig. 2). The one patient in whom intraoperative endotoxaemia in both portal and systemic blood was proved had a normal graft function and an uneventful postoperative course. Even though we did not observe endotoxaemia, we cannot exclude the occurrence of translocation completely. First, pre- or perioperative administration of antibiotics and the use of SDD may have reduced the viability and number of enteric micro-organisms; in addition, binding of polymyxin to the lipid A portion of endotoxin may have prevented absorption of endotoxin from the gut [27, 28]. Second, portal and systemic blood may have been inappropriate sources to detect endotoxin. In liver transplantation in rats, bacteria were translocated to mesenteric lymph nodes within 20 min of portal vein occlusion [29]. Similarly, translocation of bacteria to mesenteric lymph nodes has been found in humans after abdominal trauma, however, without being associated with postoperative complications [30].

When interpreting mucosal acidosis the effects of systemic disturbances in acid–base balance on pH$_i$ have to be considered. It has been suggested that in the presence of systemic acidosis the difference between arterial and mucosal pH, the "pH$_i$ gap", would more accurately reflect changes in mucosal pH originating from regionally inadequate mucosal oxygenation [31]. In our study, we did not calculate the pH$_i$ gap, because this index has never been validated as an independent measure for the adequacy of mucosal oxygenation. Although it is conceivable that pH$_i$ decreases when systemic acidosis emerges, the fact that pH$_i$ in our patients increased rapidly after reperfusion of the graft while arterial pH remained low supports the concept that pH$_i$ primarily reflects local hydrogen ion production caused by anaerobic metabolism (fig. 2). Moreover, theoretical considerations suggest that mucosal acidosis is caused by local generation of hydrogen ions from anaerobic metabolism rather than stagnation of carbon dioxide removal as mucosal blood flow decreases [25].

To avoid the confounding effects of different blood-gas analysers while interpreting pH$_i$ values, we used the same blood-gas analyser, ABL 520 (Radiometer), in the OR and ICU [32]. This device has been shown to measure $P\text{CO}_2$ accurately in saline [31].

The hypothesis that VVB would mitigate the reduction in pH$_i$ was not strictly tested in this study. To estimate accurately the effects of preserved portal blood flow on mucosal oxygenation, it would have been necessary to compare OLT performed with and without VVB in a randomized study. However, because at the time this study was performed VVB was used routinely at our institution, we could not implement a randomized study design. Although we cannot exclude the possibility that pH$_i$ may have decreased to even lower values without the use of VVB, the finding of impaired mucosal oxygenation while portal blood flow was maintained suggests that additional mechanisms must account for the preservation of mucosal perfusion during OLT.

Acknowledgement

We gratefully acknowledge Mr P. Hiltl for technical assistance and Miss Gabi Gröger for her excellent support in measuring plasma endotoxin concentrations.

References

1. Estrin JA, Belani KG, Ascher NL, Lura D, Payne W, Najarian JS. Hemodynamic changes on clamping and unclamping of major vessels during liver transplantation. *Transplantation Proceedings* 1989; **21**: 3500–3505.
2. Steib A, Freys G, Gohard R, Curzola U, Ravanello J, Lutun P, Boudjema K, Otteni J-C. Tissue oxygenation during liver transplantation. *Critical Care Medicine* 1992; **20**: 977–983.
3. Fiddian-Green RG, Baker S. Predictive value of the stomach wall pH for complications after cardiac operations: comparison with other monitoring. *Critical Care Medicine* 1987; **15**: 153–156.
4. Fiddian-Green RG, Gantz NM. Transient episodes of sigmoid ischemia and their relation to infection from intestinal organisms after abdominal aortic operations. *Critical Care Medicine* 1987; **15**: 835–838.
5. Frenette L, Doblar DD, Singer D, Cox J, Ronderos J, Poplawski S, Ranjan D. Gastric intramural pH as indicator of early allograft viability in orthotopic liver transplantation. *Transplantation* 1994; **58**: 292–297.
6. Liu L, Jeppsson B, Bengmark S. Bacterial translocation into portal blood from the gut during portal triad occlusion. *Digestive Surgery* 1992; **9**: 95–101.
7. Deitch EA. The role of intestinal barrier failure and bacterial translocation in the development of systemic infection and multiple organ failure. *Archives of Surgery* 1992; **125**: 403–404.
8. Miyata T, Yokoyama I, Todo S, Tzakis A, Selby R, Starzl TE. Endotoxaemia, pulmonary complications, and thrombocytopenia in liver transplantation. *Lancet* 1989; **1**: 189–191.
9. Yokoyama I, Todo S, Miyata T, Selby R, Tzakis AG, Starzl

TE. Endotoxemia and human liver transplantation. *Transplantation Proceedings* 1989; **21**: 3833–3841.

10. Shaw BW, Martin DJ, Marquez JM, Kang Y, Bugbee AC, Iwatsuki S, Griffith BP, Hardesty RL, Bahnson HT, Starzl TE. Venous bypass in clinical liver transplantation. *Annals of Surgery* 1984; **200**: 524–534.
11. Fiddian-Green RG, Pittenger G, Whitehouse WM. Back-diffusion of CO$_2$ and its influence on the intramural pH in gastric mucosa. *Journal of Surgical Research* 1982; **33**: 39–48.
12. Bass BL, Schweitzer EJ, Harman JW, Kraimer J. Intraluminal pCO$_2$: A reliable indicator of intestinal ischemia. *Journal of Surgical Research* 1985; **39**: 351–360.
13. Antonsson JB, Boyle CC, Kruithoff KL, Wang H, Sacristan E, Rothschild HR, Fink M. Validation of tonometric measurement of gut intramural pH during endotoxinemia and mesenteric occlusion in pigs. *American Journal of Physiology* 1990; **258**: G519–G523.
14. Grum CM, Fiddian-Green G, Pittenger GL, Grant BJB, Rothman ED, Dantzker DR. Adequacy of tissue oxygenation in intact dog intestine. *Journal of Applied Physiology* 1984; **56**: 1065–1069.
15. Frey L, Kesel A, Prückner S, Pacheco A, Messmer K. Ist der intramukosale pH Wert ein geeigneter Parameter zur Messung der Gewebeoxygenierung? *Anaesthesist* 1993; **42** (Suppl. 1): S319.
16. Fiddian-Green RG, Amelin PM, Herrmann JB, Arous E, Cutler BS, Schiedler M, Wheeler B, Baker S. Prediction of the development of sigmoid ischemia on the day of aortic operations. *Archives of Surgery* 1986; **121**: 654–660.
17. Andersen LW, Landow L, Baek L, Jansen E, Baker S. Association between gastric intramucosal pH and splanchnic endotoxin, antibody to endotoxin, and tumor necrosis factor-α concentrations in patients undergoing cardiopulmonary bypass. *Critical Care Medicine* 1993; **21**: 210–217.
18. Gutierrez G, Palizas F, Doglio G, Wainsztein N, Gallesio A, Pacin J, Dubin A, Schiavi E, Jorge M, Pusajo J, Klein F, San Roman E, Dorfman B, Shottlender J, Giniger R. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet* 1992; **339**: 195–199.
19. Marik PE. Gastric intramucosal pH: a better predictor of multiorgan dysfunction syndrome and death than oxygen-derived variables in patients with sepsis. *Chest* 1993; **104**: 225–229.
20. Unertl K, Ruckdeschel G, Jensen U, Forst H, Lenhart FP, Peter K. Prevention of colonization and respiratory infections in long term ventilated patients by antimicrobial prophylaxis. *Intensive Care Medicine* 1987; **13**: 106–113.
21. McTavish D, Buckley MM-T, Heel RC. Omeprazole; an updated review of its pharmacology and therapeutic use in acid-related disorders. *Drugs* 1991; **42**: 138–170.
22. Kratzer MAA, Belluci S, Caen JP. Detection of abnormal platelet functions with an in vitro model of primary haemostasis. *Haemostasis* 1985; **15**: 363–370.
23. Fiddian-Green RG, Stanley JC, Nostrant T, Phillips D. Chronic gastric ischemia—A cause of abdominal pain or bleeding identified from the presence of gastric mucosal acidosis. *Journal of Cardiovascular Surgery* 1989; **30**: 852–859.
24. Uusaro A, Ruokonen E, Takala J. Gastric mucosal pH does not reflect changes in splanchnic blood flow after cardiac surgery. *British Journal of Anaesthesia* 1995; **74**: 149–154.
25. Gutierrez G. Recent advances in gastric tonometry. In: Vincent, J-L ed. *Year Book of Intensive Care and Emergency Medicine*, Berlin, Heidelberg, New York, London, Paris, Tokyo, Hong Kong, Barcelona, Budapest: Springer, 1994; 200–216.
26. Downing A, Cottam S, Beard C, Potter D. Gastric mucosal pH predicts major morbidity following orthotopic liver transplantation. *Transplantation Proceedings* 1993; **25**: 1804.
27. Deitch ED, Morrison J, Berg R, Specian RD. Effect of hemorrhagic shock on bacterial translocation, intestinal morphology, and intestinal permeability in conventional and antibiotic-decontaminated rats. *Critical Care Medicine* 1990; **18**: 529–536.
28. Reed LL, Martin M, Manglano R, Newson B, Kocka F, Barrett J. Bacterial translocation following abdominal trauma in humans. *Circulatory Shock* 1994; **42**: 1–6.
29. Alexander JW, Boyce ST, Babcock GF, Gianotti L, Peck MD, Dunn DL, Pyles T, Childress CP, Ash SK. The process of microbial translocation. *Annals of Surgery* 1990; **212**: 496–512.
30. Fiddian-Green RG. Management of gastric intramucosal acidosis. In: Vincent J-L, ed. *Yearbook of Intensive Care and Emergency Medicine*. Berlin, Heidelberg, New York, London, Paris, Tokyo, Hong Kong, Barcelona, Budapest: Springer, 1994; 217–224.
31. Riddington D, Venkatesch KB, Clutton-Brock T, Bion J. Measuring carbon dioxide tension in saline and alternative solutions: quantification of bias and precision in two blood gas analyzers. *Critical Care Medicine* 1994; **22**: 96–100.
32. Takala J, Parviainen I, Siloaho M, Ruokonen E, Hämäläinen E. Saline Pco$_2$ is an important source of error in the assessment of gastric intramucosal pH. *Critical Care Medicine* 1994; **22**: 1877–1879.

British Journal of Anaesthesia 1996; **76**: 99–105

LABORATORY INVESTIGATIONS

Nitrous oxide or halothane, or both, fail to suppress c-*fos* expression in rat spinal cord dorsal horn neurones after subcutaneous formalin

W. Z. SUN, B. C. SHYU AND J. Y. SHIEH

Summary

In rats injected s.c. with formalin, behavioural correlates of the amount and pattern of Fos-like immunoreactivity (Fos-LI) (molecular responses to pain) were studied to test if early phase treatment with 75% nitrous oxide or 2% halothane, or both, suppressed subsequent spinal sensitization. Rats were allocated to four treatment groups: (1) 100% oxygen (control, $n = 15$), (2) 75% nitrous oxide (0.5 MAC, $n = 12$), (3) 2% halothane (1 MAC, $n = 12$), and (4) 75% nitrous oxide with 2% halothane (1.5 MAC, $n = 18$) for 20 min. Each rat then received a s.c. injection of 1% formalin 50 µl into the left hindpaw and anaesthesia was maintained for another 5 min (early phase). A fifth group of rats receiving fentanyl 100 µg kg^{-1} ($n = 12$) 10 min before formalin injection were studied simultaneously as a positive control. Rats in all groups were killed 60 min after formalin injection and maximal counts of Fos-LI labelled neurones in the dorsal horn of the rat spinal cord were compared according to laminar distribution. Formalin-induced behavioural hyperalgesia during the early phase was suppressed completely by fentanyl, 75% nitrous oxide, or 2% halothane, or both. The late phase response was attenuated by all four anaesthetic regimens within 20 min after injection, whereas behavioural scores for the nitrous oxide, halothane, or both, groups were nearly identical to the control 20 min later. Fentanyl suppressed the late phase response until 30 min after formalin injection but failed to reduce it thereafter. The numbers of Fos-LI labelled neurones for groups given nitrous oxide, or halothane, or both, were identical to the control, whereas numbers for fentanyl were 47.2% less ($P < 0.01$). The decrease occurred predominantly in the neck of the dorsal horn (44.9% of control, $P < 0.01$) and also in the nucleus proprius and superficial laminae (54.4% and 56.2% of control, $P < 0.05$). In summary, we found that nitrous oxide, or halothane, or both, did not suppress subsequent spinal sensitization to noxious stimulation. This result supports the previous hypothesis that inhalation anaesthesia lacks pre-emptive analgesic action. Inhalation anaesthetic agents, unlike fentanyl, suppress the early and late phase response because of anaesthetic but not analgesic effects. Thus, we suggest that measuring the genetic product of c-*fos* proto-oncogene is a useful adjunct to pharmacological tests whenever behavioural hyperalgesia is questionable or unobtainable. (*Br. J. Anaesth.* 1996; **76**: 99–105)

Key words

Analgesia, pre-emptive. Anaesthetics gases, nitrous oxide. Anaesthetics volatile, halothane. Anaesthetics i.v., fentanyl. Rat. Genetic factors, proto-oncogenes.

Inhalation anaesthetics are considered poor analgesics despite potent anaesthetic actions in producing surgical immobility. Wall hypothesized that lightly anaesthetizing the spinal cord fails to block the afferent signals set off during surgery, and that other treatments such as regional anaesthesia before skin incision are required to produce significant pre-emptive analgesia during inhalation anaesthesia [1]. The concept that prevention of intense nociceptor activation can suppress the subsequent hyperalgesic state has had a major impact on the practice of postoperative analgesia [2]. Although pre-emptive analgesia is well documented in animal models, the clinical evidence is less convincing [3]. A critical difference between humans and animal models is the method of pain assessment. In animal models, the sensitivity and specificity of behavioural responses as an index of nociception largely remain to be determined.

In contrast with previous hypotheses, recent studies based on formalin-induced behavioural hyperalgesia have demonstrated mild to moderate pre-emptive analgesia after volatile agents (i.e. halothane and isoflurane) [4, 5]. Paradoxically, this response was not found in rats receiving nitrous oxide with halothane, although their combined anaesthetic potency is greater than that of each agent alone. In a parallel study, nitrous oxide, but not halothane, induced dose-dependent pre-emptive analgesia that was partially reversed by naloxone and halothane [6]. The results of these studies vary

---

WEI-ZEN SUN*, MD (Department of Anesthesiology); JENG-YUNG SHIEH, PHD (Department of Anatomy); Medical College of National Taiwan University, Taipei, Taiwan. BAI-CHUANG SHYU, PHD, Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan. Accepted for publication: July 7, 1995.

*Address for correspondence: Department of Anaesthesiology, National Taiwan University Hospital, No. 7, Chungshan South Road, Taipei, Taiwan, ROC.

This article is accompanied by an Editorial.

markedly despite identical variables being used. As discrepancies may occur as a result of general attenuation of behaviour because of the non-algesic effect of anaesthetics but not their analgesic effect [7], a further index is required to examine the analgesic effect of inhalation anaesthetics.

Unlike most physiological indices of pain, *c-fos* expression in the brain is least affected by various i.v. and inhalation anaesthetics [8–10]. The genetic products of *c-fos* expression are highly associated with neuronal sensitization in the central nervous system and with behavioural hyperalgesia [11]. The number of Fos-like immunoreactivity (Fos-LI) labelled neurones has been used widely to quantify the antinociceptive action of various analgesic agents [12, 13]. Various patterns of suppression for subpopulations of spinal nociceptive neurones may provide further understanding on how the antinociceptive process is involved [14]. By providing both qualitative and quantitative indices for pain, Fos-LI has been accepted as a morphological marker to assess the effectiveness of analgesia [15, 16]. In the present study we used Fos-LI as a biochemical correlate of behavioural indices to test if pre-stimulus inhalation anaesthesia with nitrous oxide or halothane, or both, differentially suppressed the subsequent spinal sensitization in the rat formalin model. To study the possible mechanism of the behavioural response, fentanyl was used as a positive control for analgesia.

Materials and methods

The studies were approved by the Institutional Animal Care Subcommittee of the National Taiwan University Hospital. Male Sprague–Dawley rats, weighing 300–350 g, were maintained in a 12-h light–dark cycle and allowed free access to food and water. Experiments were performed between 10:00 and 16:00 in a randomized order. Rats were allocated randomly to one of five groups: (1) control (100 % oxygen, $n = 15$), (2) 75 % nitrous oxide (0.5 MAC, $n = 12$), (3) 2 % halothane (1 MAC, $n = 12$), (4) 75 % nitrous oxide with 2 % halothane (1.5 MAC, $n = 18$), and (5) fentanyl 100 µg kg^{-1} in 100 % oxygen ($n = 12$). Two phases of response were defined: early (0–5 min) and late (5–60 min) [17]. The inspired concentrations of nitrous oxide and halothane (75 % and 2 %) were chosen to provide approximately 0.5 and 1 MAC of anaesthesia, respectively. These doses were calculated on the basis of MAC, 148–150 % for nitrous oxide and 0.95–1.11 % for halothane [18], and an estimated ratio of end-tidal-to-inspired concentration of halothane of 0.5–0.6 in spontaneously breathing rats after 20 min [19]. Anaesthesia was induced by placing the animals in a Plexiglas box prefilled and flushed continuously at 4 litre min^{-1} with one of the anaesthetics. Except for rats in the fentanyl group, which were given fentanyl 100 µg kg^{-1} i.p. 10 min before formalin, animals were left undisturbed for 20 min and then removed briefly from the box for injection of formalin. To ensure an adequate anaesthetic level on injection, rats receiving halothane and nitrous oxide–halothane were subject to further anaesthesia until the corneal reflex and withdrawal to forceful pinch of the forepaw were absent. Animals were returned to the box immediately after injection and maintained under anaesthesia for another 5 min (early phase). Rats were then transferred to a clear open cage and allowed to recover, and their behaviour was observed by a blinded observer for 60 min after formalin injection (late phase). During the recovery phase from inhalation anaesthesia, the forepaw was pinched every 30 s to monitor the level of anaesthesia until spontaneous movement occurred. All gas concentrations were monitored continuously and maintained at the desired level with an attached gas analyser (RGM 5250 Ohmeda, Madison).

FORMALIN TEST

Diluted (1 %) formalin was prepared freshly from 37 % formaldehyde with 0.9 % normal saline before use; 50 µl was injected s.c. into the plantar surface of the left hindpaw using a 26-gauge needle. With a computer program designed by one of the authors (B.C.S.), the amount of time spent in each of four behavioural categories, 0–3, was recorded and calculated every minute, as described by Dubuisson and Dennis [20]. In brief, the categories were: 0 = the injected paw is not favoured (i.e. foot flat on floor with toes splayed); 1 = the injected paw has little or no weight on it with no toe splaying; 2 = the injected paw is elevated and the heel is not in contact with any surface; 3 = the injected paw is licked, bitten or shaken. The scores were then averaged at 5-min intervals. To investigate further the temporal pattern of behavioural responses, the scores were summed for six time intervals: 5–60, 10–60, 20–60, 30–60, 40–50 and 50–60 min, respectively. The summed score was used to facilitate comparison of behaviour with the amount of Fos-LI produced over 0–60 min after injection.

IMMUNOHISTOCHEMISTRY

All animals were killed 60 min after formalin injection. Animals were anaesthetized deeply with an overdose of sodium pentobarbitone and perfused transcardially with saline followed by 4 % paraformaldehyde in phosphate buffer 0.1 mol litre^{-1} (pH = 7.4). The spinal cord at the lumbar enlargement was removed, post-fixed for 4 h, and cryoprotected overnight in 30 % sucrose. Frozen sections were cut in a cryostat (30 µm) and collected as free-floating sections. Sections were incubated with primary rabbit polyclonal anti-Fos antiserum (Ab-2, Oncogene), diluted 1:750 with PBS 0.1 mol litre^{-1}, containing 3 % normal goat serum (NGS) and 0.3 % Triton X-100 for 48 h at 4 °C. After being washed in PBS, they were incubated with biotinylated second antibody (goat anti-rabbit antiserum; Vector) diluted 1:200 in PBS for 1 h at room temperature. Sections were reacted with elite ABC (Vectastain) diluted 1:50 for 1 h and then 0.1 % diaminobenzidine solution containing 0.6 % nickel ammonium sulphate and 0.2 % H_2O_2 as substrate was added. All sections were mounted on gelatin-subbed slides, air-dried and protected with a coverslip for light microscopic inspection. Two additional groups of rats, one of which received 75% nitrous oxide with 2% halothane but not formalin injection ($n = 2$), and other which received neither gas nor formalin ($n = 2$), were studied as negative controls for non-specific staining caused by either inhalation anaesthetics or animal manipulation. To examine the specificity of the primary antibody, non-specific staining was tested simultaneously for the control rats. Omission of the anti-c-*fos* antibody was prepared by immunoprecipitation with c-*fos* peptide (Oncogene) before the primary antibody reaction. Dark staining of the nucleus, as shown in the section treated with antibody alone, was completely absent. This approach ensured high quality of specificity for the antibody in use.

COUNTING OF FOS-LI LABELLED NEURONES

Fos-LI labelled neurones were examined throughout the L3–5 spinal segments and across the laminae. Sections were examined using a dark-field microscope (Axioscope, Zeiss) to determine the segmental level according to the grey matter landmarks, as described by Molander, Xu and Grant [21]. Under dark-field illumination, the dorsal horn of each section was divided further into three regions: (1) the superficial laminae (laminae I/II), (2) the nucleus proprius (laminae III/IV) and (3) the neck (laminae V/VI) [14]. Fos-LI labelled neurones were then examined with bright-field illumination at 100× magnification for each section. All images, in both dark- and bright-field illumination, were printed serially on glossy thermal paper via a connected CCD camera (Videl Lens, Cohu) and video copy processor (P67U, Mitsubishi). Fos-LI labelled neurones, which showed deep staining distinguishable from background, were counted from the printed images with respect to each lamina. To minimize further the individual bias for inspection, all images were duplicated and counted separately by two experienced laboratory assistants throughout the study. When the difference between duplicated counting was greater than 10% of each lamina, a third copy was made and inspected by one of the authors (W.Z.S.) Counts that were questionable in either quantity or quality were excluded. At least 10–15 sections were scanned for each segment, and three sections with the greatest number were selected. The observers who scored formalin-induced behavioural hyperalgesia and investigators who counted Fos-LI labelled neurones were all blind to the treatment of each animal.

DATA ANALYSIS

Statistical analysis was performed to compare the different groups of animals, using one-way analysis of variance (ANOVA) for the pain score at each time point and for the total number of Fos-LI labelled neurones, and two-way repeated measure ANOVA (treatment × lamina) for the number of labelled neurones and the laminar region. The Student–Newman–Keuls test was used for multiple comparisons. $P < 0.05$ was considered statistically significant.

Results

BEHAVIOURAL RESPONSES

S.c. injection of 1% formalin produced a similar biphasic pain response in the control group to that described by Dubuissen and Dennis [20]. A brief phase of intense pain (i.e. licking, biting and flinching of the injected paw) occurred in the first 5 min. Pain then subsided for 10 min, and a later phase

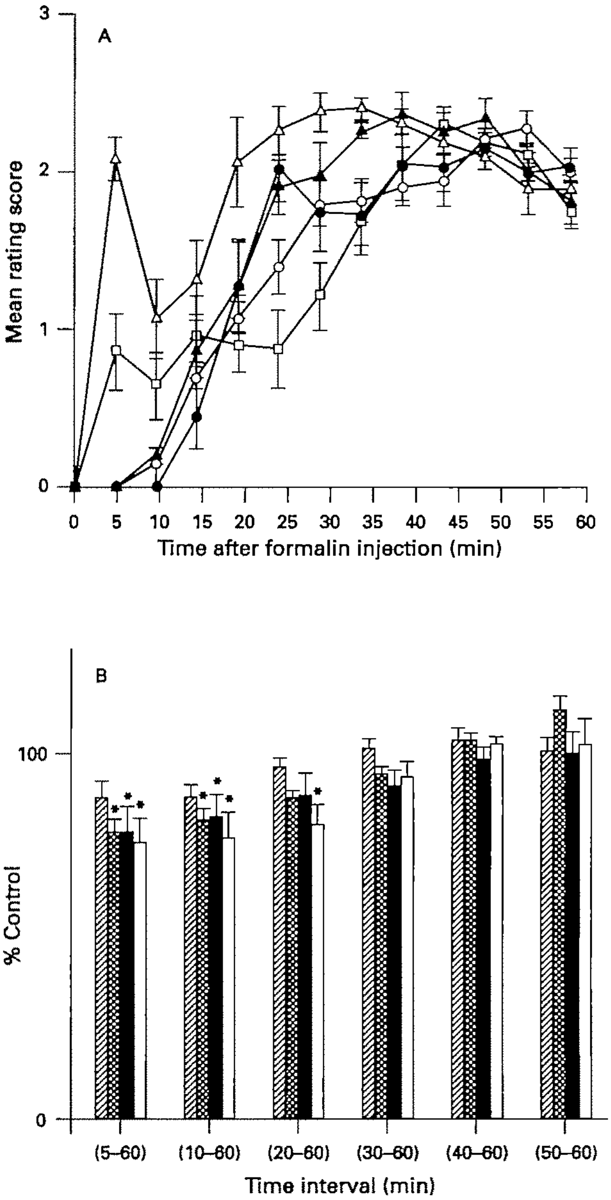


Figure 1. Time course of anaesthetic effects on formalin-induced pain score (mean, SEM). A: Pain score × minute plotted as a function of time after injection of formalin in the control (△), 75% nitrous oxide (▲), 2% halothane (○), 75% nitrous oxide with 2% halothane (●) and fentanyl 100 µg kg^{-1} (□) groups. B: Ratio of summed score in the experimental groups to control group (% of control) plotted as a function of time. ▨ = Nitrous oxide 75%, ▩ = 2% halothane, ■ = 75% nitrous oxide with 2% halothane and □ = fentanyl 100 µg kg^{-1}. * $P < 0.05$ compared with control.

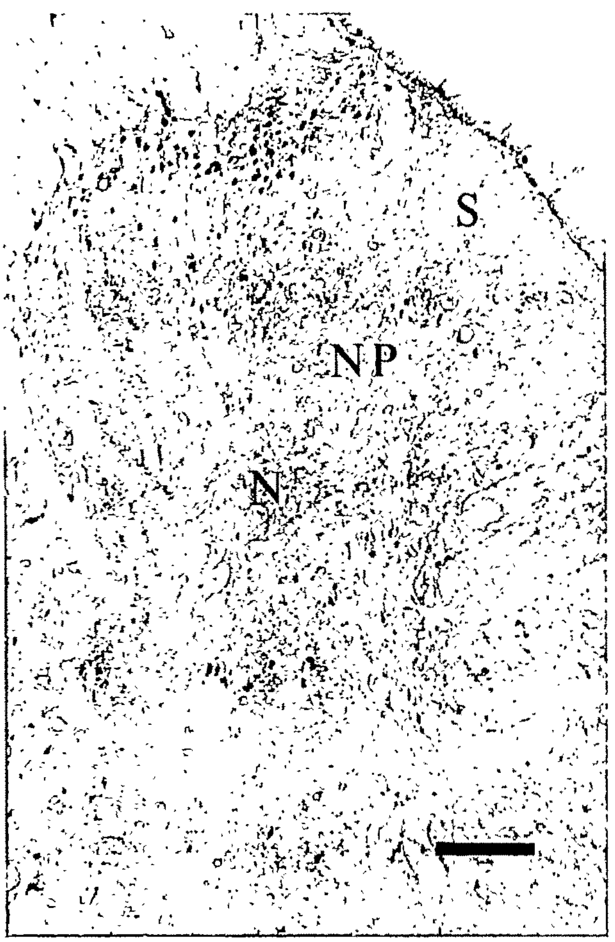


Figure 2. Fos-LI distribution in the dorsal horn of the L4 segment ipsilateral to the formalin injection in the control group. S = Superficial laminae, NP = nucleus proprius, N = neck of the dorsal horn. Scale bar = 100 μm.

of moderate pain (i.e. elevation of the injected paw) was expressed from 20 to 60 min. Peak pain score occurred 30 min after injection (fig. 1A). In rats receiving fentanyl, or nitrous oxide or halothane, or both, behaviours such as elevation, biting, shaking and flinching of the injected paw were absent during the early phase. Most rats recovered from inhalation anaesthesia, as shown by responding to painful pinch stimulation within 5 min after anaesthesia, and this was followed by a quiescent period, that is a period without any characteristic pain behaviour. Steady gait and investigatory behaviours (e.g. rearing) persisted for 10–15 min and were followed by a short period of shaking and biting of the injected paw. For rats receiving fentanyl 100 μg kg^{-1}, a variable degree of rigidity was observed on formalin injection and maintained for approximately 30 min thereafter with attenuated behavioural hyperalgesia.

Summations of the pain scores from various time intervals were compared to investigate the overall behavioural response to the formalin test (fig. 1B). At the 5–60-min interval, the score for the nitrous oxide group was identical to that for the control group, while scores for fentanyl (24 %, $P < 0.01$), halothane (18 %, $P < 0.05$), and nitrous oxide–halothane groups (17 %, $P < 0.05$) were significantly lower. Starting from 20 min after injection, summed scores for all gas groups were indistinguishable ($P > 0.05$), indicating that inhalation anaesthesia attenuated pain scores for 20 min after injection. The score for the fentanyl group was 19 % less than the control score ($P < 0.05$) at the 20–60-min interval, whereas no difference for all groups was found at 30–60, 40–60 and 50–60 min. Despite full recovery, many rats fell asleep for the rest of the time. With the injected paw held dorsiflexed tonically, the rats lay on the uninjected side to avoid accidentally touching the ground.

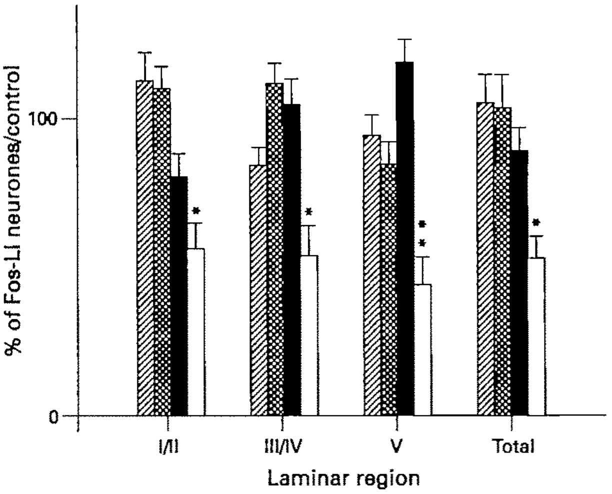


Figure 3. Effects of anaesthesia on the expression of Fos-LI labelled neurones in each laminar region (mean, SEM percentage of control). Ratio of Fos-LI labelled neurones in experimental groups to control group plotted at each lamina: I/II = superficial laminae, III/IV = nucleus proprius, V = neck of the dorsal horn. ▨ = Nitrous oxide 75 %, ▩ = 2 % halothane, ■ = 75 % nitrous oxide with 2 % halothane and □ = fentanyl 100 μg kg^{-1}. * $P < 0.05$, ** $P < 0.01$ compared with control.

COUNTING OF FOS-LI LABELLED NEURONES

Fos-LI labelled neurones were distinguished readily by their dark blue nucleus and scant staining of the cytoplasm. In control rats injected with 1 % formalin, numerous Fos-LI labelled neurones were observed in the superficial laminae and neck of the dorsal horn. These neurones were concentrated exclusively on the side ipsilateral to the injected paw. The most dense concentration of Fos-LI neurones, 48.3 (6.5) per section, occurred in the superficial laminae (fig. 2). Modest numbers of labelled neurones were observed in the neck of the dorsal horn, 19.4 (6.5) per section. Fewer Fos-LI neurones, 8.9 (3.2) per section, were observed in the nucleus proprius. Fos-LI labelled neurones in the negative control rats were found occasionally (less than 5 per section) suggesting that inhalation anaesthesia *per se* failed to enhance c-*fos* expression. Significant differences were evident across the five groups ($P < 0.05$), and across spinal cord laminae ($P < 0.01$). These differences were the result of a pronounced decrease in the fentanyl group. Fentanyl reduced overall numbers of Fos-LI labelled neurones (56 % of control, $P < 0.05$). Suppression of Fos-LI occurred in the superficial lamina (61 % of control, $P < 0.05$), nucleus proprius (46 % of control, $P < 0.05$) and the neck (39 % of control, $P < 0.01$) (fig. 3). None of the rats receiving inhalation anaesthesia had reduced numbers of Fos-LI labelled neurones ($P > 0.05$).

Discussion

We have demonstrated that inhalation anaesthesia with 75% nitrous oxide or 2% halothane, of both, failed to suppress formalin-induced behavioural hyperalgesia in the late phase (20–60 min after injection) and the expression of *c-fos* proto-oncogene, a molecular index of spinal sensitization to pain. Both behavioural and biochemical evidence demonstrated a lack of pre-emptive analgesic effect of inhalation anaesthesia at 0.5–1.5 MAC. Our results clearly contradict previous studies showing a modest reduction in late phase behavioural hyperalgesia using the same experimental paradigms but with a lower anaesthetic potency (30–75% nitrous oxide, 0.7–1.8% halothane, 1–2.5% isoflurane) [4–6]. The major difference between previous studies and ours is the behavioural index used to quantify formalin-induced hyperalgesia. Abram and Yaksh [4] and Goto, Marota and Crosby [6] counted the occurrence of flinch behaviour, whereas a mean rating score was used in our study. Although flinch is generally believed to be more robust and spontaneous [22], none of these studies compared flinching with mean rating score. Moreover, the stability and reliability of these behavioural measurements have never been proved under general anaesthesia. In the present study, we have shown the limitation of using behavioural observation to detect antinociceptive effect by inhalation anaesthesia. For a similar degree of suppression of behavioural response, fentanyl reduced the number of Fos-LI labelled neurones whereas inhalation anaesthesia did not. Thus, attenuation of formalin-induced behavioural hyperalgesia may occur as a result of analgesic in addition to non-analgesic effects.

The reason why we used a mean rating score was because of variable responses in previous studies that used flinch behaviour. Abram and Yaksh [4] demonstrated a modest reduction in the late phase whereas no decrease was found by Goto, Marota and Crosby [6]. Furthermore, Goto, Marota and Crosby showed that 0.9% halothane suppressed early phase flinch only partially whereas O'Connor and Abram demonstrated that 0.7% halothane completely suppressed it [5]. These results, together with ours, are a clear demonstration of how behavioural observations can vary markedly whether or not a similar variable is used. Mean rating score was thus chosen by us to avoid further confusion. One possible explanation of the discrepancy between previous studies and ours is the occurrence of flinch that may be more susceptible to prolonged amnesia after 25 min of exposure to 0.5–1.5 MAC of anaesthesia. It has been shown that single-variable measures of formalin-induced nociceptive behaviours, such as flinching or licking, are likely to be influenced by pharmacological agents which either stimulate or depress locomotor activity or cause competing stereotypic behaviours [23]. Although no residual anaesthetic effect was present during the late phase, many rats remained asleep despite full recovery from anaesthesia, as shown by painful pinch. It is unlikely that the hypnotic property of inhalation anaesthesia outlasts its anaesthetic property. Hence, potentiation of the normal sleep cycle during observation (10:00–16:00) may explain the cause of prolonged sleep. However, the lingering effect of residual gases on flinch is not supported by Abram and Yaksh [4] who found that continuous exposure to 0.25% isoflurane during the late phase failed to reduce flinch responses. This, again, does not explain the pre-emptive analgesia effect of 75% nitrous oxide (0.5 MAC) and not 0.9% halothane with or without 75% nitrous oxide (0.5–1 MAC), became nitrous oxide is less soluble in blood and so should have less of an effect in rats. Another explanation for our results is the use of a different concentration of formalin; 1% compared with 5% in previous studies. It has been shown that some behavioural responses, for example flinching and licking, are more common after 5% formalin [24]. Thus to use flinch as a dependent measure in a rat model, one must use a high concentration of formalin (5%) to obtain a meaningful level of response. However, this is inconsistent with the recent understanding that low formalin concentrations (0.5–2.5%) have the advantage of increasing the sensitivity of the test [7]. Detection of the effect of weak analgesics is facilitated by eliminating the problem of a ceiling effect, and it is furthermore possible to detect a state of hyperalgesia [17, 25]. We believe 1% formalin is more sensitive than 5% in detecting the weak, if any, analgesic effect of general anaesthesia.

A potential advantage of Fos-LI is its usefulness in determining the most appropriate times for comparison. Pain scores for all treatment groups were significantly less than for the control within 20 min after injection (i.e. 5–60 and 10–60 min, respectively). However, scores for all anaesthetics were indistinguishable after 20 min (i.e. 20–60, 30–60, 40–60 and 50–60 min, respectively). As no suppression of Fos-LI was found for rats receiving inhalation anaesthesia, we suggest that the behavioural response within 20 min after anaesthesia should be disregarded. It makes no difference if a brief period (e.g. 50–60 min) or a longer period (e.g. 20–60 min) is used. On the other hand, fentanyl produced suppression of the late phase response within 30 min after injection but no suppression thereafter. Comparison of its antinociceptive effect must therefore include the initial response (e.g. 5–60, 10–60 and 20–60 min). Thus, the behavioural response at the 20–60-min time period, a significantly lower pain score by fentanyl, and an identical score by all anaesthetic gases, are comparable to the molecular index of spinal sensitization. Despite the fact that behavioural responses to formalin test and postoperative pain vary greatly with time, potential bias from selecting an appropriate time interval for comparison is overlooked by most investigators. Various times between 5 and 75 min after injection are chosen, for example, 10–60 min (Abram and Yaksh [4]) and 30–75 min (Goto, Marota and Crosby [6]). No comparative study has been performed to explain how the specific times were chosen. Using Fos-LI as a molecular correlate of behavioural hyperalgesia, this is the first study to describe why and how the specific times were chosen.

Despite being used extensively as a quantitative tool for nociception, the physiological role of the c-*fos* gene product in the spinal cord dorsal horn remains to be determined. c-*fos* expression in the neurones is produced by either noxious or non-noxious stimulation. Non-noxious stimuli, such as brushing and manipulation of the hindlimb, evoke a moderate increase in Fos-LI in areas of the spinal cord (laminae III/VI) that receive primarily non-nociceptive afferents [26]. Without nociceptive input, walking on a rotating rod produces a large increase in Fos-LI and c-*fos* mRNA level, while the pattern of labelled neurones is distinct from that produced by noxious stimulation [14]. Under controlled stimulus conditions, it is well documented that the pattern of Fos-LI distribution is related to nociception [27]. However, non-noxious stimulation (e.g. itching) can also evoke a similar pattern of c-*fos* expression [28]. Hence, the use of biochemical markers for pain measurement must be strictly designed and carefully evaluated. Furthermore, c-*fos* expression is a result of temporal summation over time. Lack of resolution at any specific time point may greatly limit the use of this method. We suggest that c-*fos* expression should never replace behavioural observation in pain assessment. Instead, it should be accepted as a useful adjunct to behavioural observation when correctly designed.

In summary, both our molecular and behavioural indices demonstrated that pre-emptive analgesia was *lacking* after inhalation anaesthesia, regardless of gas and anaesthetic potency. Our study failed to confirm previous findings that isoflurane [4], halothane [5] and nitrous oxide [6] produced moderate pre-emptive analgesia, and thus in turn supports the hypothesis that general anaesthesia fails to block the afferent signals set off during intense surgical pain. The differential Fos-LI response between fentanyl and general anaesthesia suggests that suppression of behavioural hyperalgesia may occur as a result of analgesic and non-analgesic effects. Thus behavioural response as an index for nociception must be evaluated carefully during and immediately after general anaesthesia. We suggest c-*fos* expression is a useful adjunct to pharmacological tests whenever behavioural observation is questionable or unobtainable.

Acknowledgements

We thank Dr L. C. See for her assistance with statistical analysis and Dr C. Fletcher for revision of the manuscript. We also thank Professor Emeritus S. H. Ngai, Columbia University for his critical reviews and valuable comments. The study was supported in part by grant NSC81-0412-B00265-4 from the National Science Council, Taiwan and by grant AS-NTUH-CRC92-106 from the Institute of Biomedical Sciences, Academia Sinica, Taiwan.

References

1. Wall PD. The prevention of postoperative pain. *Pain* 1988; 33, 289–290.
2. Woolf CJ, Chong MS. Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. *Anesthesia and Analgesia* 1993; **77**: 362–379.
3. Johansson B, Glise H, Hallerback B, Dalman P, Kristoffersson A. Preoperative local infiltration with ropivacaine for postoperative pain relief after cholecystectomy. *Anesthesia and Analgesia* 1994; **78**: 210–214.
4. Abram SE, Yaksh TL. Morphine, but not inhalation anesthesia, blocks post-injury facilitation. The role of preemptive suppression of afferent transmission. *Anesthesiology* 1993; **78**: 713–721.
5. O'Connor TC, Abram SE. Halothane enhances suppression of spinal sensitization by intrathecal morphine in the rat formalin test. *Anesthesiology* 1994; **81**: 1277–1283.
6. Goto T, Marota JJ, Crosby G. Nitrous oxide induces preemptive analgesia in the rat that is antagonized by halothane. *Anesthesiology* 1994; **80**: 409–416.
7. Tjolsen A, Berge OG, Hunskar S, Rosland JH, Hole K. The formalin test: an evaluation of the method. *Pain* 1992; **51**: 5–17.
8. Takayama K, Suzuki T, Miura M. The comparison of effects of various anaesthetics on expression of Fos protein in the rat brain. *Neuroscience Letters* 1994; **176**: 59–62.
9. Tolle TR, Schadrack J, Castro-Lopes JM, Evan G, Roques BP, Zieglgansberger W. Effects of kelatorphan and morphine before and after noxious stimulation on immediate–early gene expression in rat spinal cord neurones. *Pain* 1994; **56**: 103–112.
10. Marota JJA, Crosby G, Uhl GR. Selective effects of pentobarbital and halothane on c-*fos* and *jun-B* gene expression in rat brain. *Anesthesiology* 1992; **77**: 365–371.
11. Dubner R, Ruda MA. Activity-dependent neuronal plasticity following tissue injury and inflammation. *Trends in Neurosciences* 1992; **15**: 96–103.
12. Tolle TR, Herdegen T, Schadrack J, Bravo R, Zimmermann M, Zieglgansberger W.. Application of morphine prior to noxious stimulation differentially modulates expression of Fos, Jun and Krox-24 proteins in rat spinal cord neurones. *Neuroscience* 1994; **58**: 305–321.
13. Pertovaara A, Bravo R, Herdergen T. Induction and suppression of immediate–early genes by selective alpha-2-adrenoreceptor agonist and antagonist in the rat brain following noxious peripheral stimulation. *Neuroscience* 1993; 54, 117–126.
14. Presley RW, Menetrey D, Levine JD, Basbaum AI. Systemic morphine suppresses noxious stimulus-evoked Fos protein-like immunoreactivity in the rat spinal cord. *Journal of Neuroscience* 1990; **10**: 323–335.
15. Abbadie C, Honore F, Fournie-Zaluski MC, Roques BP, Besson JM. Effects of opioids and non-opioids on c-Fos-like immunoreactivity induced in rat lumbar spinal cord neurones by noxious heat stimulation. *European Journal of Pharmacology* 1994; **258**: 215–227.
16. Bullitt E. Expression of c-*fos*-like protein as a marker for neuronal activity following noxious stimulation in the rat. *Journal of Comparative Neurology* 1990; **296**: 517–530.
17. Coderre TJ, Vaccarino AL, Melzack R. Central nervous system plasticity in the tonic pain response to subcutaneous formalin injection. *Brain Research* 1990; 535: 155–158.
18. Cole, DJ, Kalichman MW, Shapiro HM, Drummond JC. The nonlinear potency of sub-MAC concentrations of nitrous oxide in decreasing the anesthetic requirement of enflurane, halothane, and isoflurane in rats. *Anesthesiology* 1990; **73**: 93–99.
19. White PF, Johnston RR, Eger EI II. Determination of anesthetic requirement in rats. *Anesthesiology* 1974; **40**: 52–57.
20. Dubuisson D, Dennis SG. The formalin test: a quantitative study of the analgesic effects of morphine, meperidine, and brain stem stimulation in rats and cats. *Pain* 1977; **4**: 161–174.
21. Molander C, Xu Q, Grant G. The cytoarchitectonic organization of the spinal cord in the rat. I. The lower thoracic and lumbosacral cord. *Journal of Comparative Neurology* 1984; **230**: 133–141.
22. Wheeler-Aceto H, Cowan A. Standardization of the rat paw formalin test for the evaluation of analgesics. *Psychopharmacology* 1991; **104**: 35–44.
23. Berge OG, Carcia-Cabrera I, Furset K. Hyperbaric exposure

and morphine alters the pattern of behaviour in the formalin test. *Pharmacology, Biochemistry and Behaviour* 1991; **40**: 197–201.

24. Coderre TJ, Fundytus ME, McKenna JE, Dalal S, Melzack R. The formalin test: a validation of the weighted-scores method of behavioural pain rating. *Pain* 1993; **54**: 43–50.
25. Abbott FV, Melzack R, Samuel C. Morphine analgesia in the tail-flick and formalin pain tests is mediated by different neural system. *Experimental Neurology* 1982; **75**: 644–651.
26. Hunt SP, Pini A, Evan G. Induction of c-*fos*-like protein in spinal cord neurones following sensory stimulation. *Nature (London)* 1987; **328**: 632–634.
27. Jasmin L, Gogas KR, Ahlgren SC, Levine JD, Basbaum AI. Walking evokes a distinctive pattern of Fos-like immunoreactivity in the caudal brainstem and spinal cord of rat. *Neuroscience* 1994; **58**: 275–286.
28. Yao GL, Tohyama M, Senba E. Histamine-caused itch induces Fos-like immunoreactivity in dorsal horn neurones: effect of morphine pretreatment. *Brain Research* 1992; **599**: 333–337.

British Journal of Anaesthesia 1996; **76**: 106–110

Effects of morphine on atrial preparations obtained from non-failing and failing human hearts

F. LLOBEL AND M. L. LAORDEN

Summary

We have examined the effects of morphine in auricular myocardium from non-failing and failing human hearts. In both preparations morphine induced inhibition. These responses were not antagonized by naloxone. Comparison of mean IC_{30} values obtained in non-failing (3.9 (SEM 0.2) $\times 10^{-8}$ mol litre^{-1}) and failing (5010 (200) $\times 10^{-8}$ mol litre^{-1}) hearts indicated that the morphine concentration–response curves were significantly ($P < 0.001$) shifted to the right in preparations from failing hearts. In addition, a decrease in the maximal response was observed. These data indicate that opioid receptors are not involved in the cardiac effects induced by morphine and that there is a decrease in responses to morphine in the failing heart. (*Br. J. Anaesth.* 1996; **76**: 106–110)

Key words

Heart, isolated preparation. Heart, myocardial function. Analgesics opioid, morphine.

It has been demonstrated that morphine induces negative inotropic and chronotropic effects on isolated left and right atria of the rat [1–3]. However, it has also been shown in different heart muscle preparations from mammalian species, including humans, that morphine fails to influence cardiac function directly [4]. Despite numerous studies, the possible mechanism involved in the cardiac inhibitory effects of this drug are controversial. Recently, it has been postulated that opioid agonists have complex cardiovascular actions. Some effects may be mediated via opioid receptors while others are independent of opioid receptors [5].

On the other hand it is known that the opioid system is involved in various stress situations such as shock [6] and heart failure [7]. Thus in acute heart failure patients, the β-endorphin, met-enkephalin, and dynorphin plasma concentrations are increased, which provides evidence of activation of the opioid system [8]. However, in patients with chronic heart failure, plasma concentrations of β-endorphin and lipotrophin are decreased, which is interpreted as exhaustion of the opioid system [9].

Despite the well known fact that opioids play a significant role in heart failure, there is little information on the cardiac action of morphine on the human heart, and no information on its effect in the failing human myocardium. Heart failure results in increased sympathetic drive with increased plasma noradrenaline concentrations [10]. Prolonged exposure of a cell to a drug usually results in reduction or down-regulation of functional cell surface receptor molecules. The mechanisms involved in receptor desensitization have been studied most extensively for the β adrenoceptor [11]. We have examined, therefore, if the failing heart alters responses to morphine, as occurs with β adrenergic agonists. Thus we have investigated the effects of morphine in isolated human right atrium from failing and non-failing human hearts and any possible involvement of opioid receptors by undertaking similar experiments in the presence of naloxone.

Materials and methods

PATIENTS

The study was approved by the Institutional Research Practices Committee. All patients gave written informed consent. The Committee of Human research also approved the study.

Human right atrial appendages were obtained from 20 patients (12 male) without apparent heart failure (mean age 50.1 (range 36–58) yr) with mitral valve disease (NYHA classes I–II). Myocardium from failing human hearts was obtained from 20 patients (14 male) (mean age 52.8 (range 40–69) yr) with severe mitral valve disease (NYHA classes III–IV). In all patients auricular muscle was obtained from tissue resected during cardiac surgery before heart cannulation preceding extracorporeal circulation. None of these patients had been treated with sympathomimetic drug or β adrenoceptor antagonists for at least 3 weeks before operation. Some patients were treated with nitrates (15), calcium antagonists (10) or diuretics (15), and occasionally with angiotensin-converting enzyme (ACE) inhibitors ($n = 8$) or digitalis glycosides ($n = 3$), alone or in combination.

General anaesthesia comprised fentanyl with benzodiazepines and isoflurane. Pancuronium was used as a neuromuscular blocker (the washout procedure described below was designed to eliminate any potential influence of these agents).

FRANCISCA LLOBEL, MD (Department of Anaesthesiology); M. LUISA LAORDEN*, MD (Department of Physiology and Pharmacology, Unit of Pharmacology, University School of Medicine); CSV Arrixaca Hospital, Murcia, Spain. Accepted for publication: August 2, 1995.

*Address for correspondence: Departamento de Farmacologia, Facultad de Medicina, Campus de Espinardo, 30071 Murcia, España.

Immediately after excision, the atrial muscle strips were placed in ice-cold pre-aerated Tyrode solution (for composition see below) and delivered to the laboratory within 15 min.

PREPARATION OF TISSUES AND ORGAN BATH EXPERIMENTS

The right atrial appendages were dissected to yield trabecula strips (4–5 mm in length and 1 mm or less in diameter) without endocardial damage and with fibres running parallel to the length of the strip.

The preparations were mounted in 10-ml organ baths at 37 °C containing a modified Tyrode's solution of the following composition (mmol litre^{-1}): NaCl 119.8; $CaCl_2$ 1.8; KCl 5.4; $MgCl_2$ 1.05; NaH_2PO_4 0.42; $NaHCO_3$ 22.6; glucose 5.05; ascorbic acid 0.28; and disodium EDTA 0.05. The bathing solution was aerated with 95 % oxygen and 5 % carbon dioxide. Myocardial strips were stimulated electrically (Grass SD-9) by two platinum ring electrodes at a frequency of 1 Hz by rectangular pulses of 10 ms and supramaximal voltage (30 V). Each preparation was suspended under a resting tension of 0.5 *g*. After suspension in the organ baths, the tissues were washed four times every 10 min. Thereafter the preparations were allowed to equilibrate for 90 min and the bathing solution was changed once after 45 min. Isometric force of contraction was measured using a force displacement transducer (Grass FT-03) and recorded on a Dynograph Beckman polygraph. Each muscle preparation was used for one concentration–response curve.

Increased concentrations of morphine were added cumulatively to the organ bath at concentrations ranging from 10^{-10} to 10^{-3} mol litre^{-1}. Each drug concentration was added to the organ bath in a volume of 0.1 ml at 5-min intervals. Concentration–response curves to morphine were obtained also in the presence of naloxone (10^{-8}, 10^{-7} or 10^{-6} mol litre^{-1}) added 15 min before morphine. Concentration–response curves were also constructed with naloxone 10^{-11}–10^{-4} mol litre^{-1} (data not shown). In the time-control groups, equal volumes of distilled water (diluent for morphine and naloxone) were added to the tissue baths at the same times as those for the morphine and morphine with naloxone groups. To evaluate heart failure, we also constructed concentration–response curves with isoproterenol 10^{-11}–10^{-5} mol litre^{-1} in preparations from non-failing and failing hearts.

The effects of morphine alone and isoproterenol are expressed as percentage change from baseline values. Similarly, the effects of morphine in the presence of naloxone are expressed as percentage change from baseline values after opioid antagonists.

STATISTICS

The results are expressed as means (SEM) of *n* experiments. Statistical comparisons were performed with one-way analysis of variance, followed by the Newman–Keuls *post hoc* test. Differences with *P* values, less than 0.05 were considered significant. IC_{30}, IC_{50} and the slope were calculated by linear regression of the log concentration plot of the data with the aid of a computer program [12]. Mean slope values were compared using Student's *t* test.

COMPOUNDS

The drugs used were morphine (Alcaliber Spain), naloxone hydrochloride (Merck, Sharp & Dohme, Spain) and isoproterenol hydrochloride (Sigma, Spain).

Results

The maximal effect on force of contraction occurred within 3–4 min after adding morphine or isoproterenol to the bath. All concentrations of isoproterenol tested significantly increased the force of contraction in a dose-related pattern compared with control. The maximal effect obtained in the non-failing heart (97.2 (3.2) %) was significantly ($P < 0.01$) higher than that obtained in the failing heart (51.2 (1.1) %). Similarly, the IC_{50} for isoproterenol was significantly ($P < 0.001$) lower in non-failing compared with failing hearts (9.3 (0.2) × 10^{-8} and 120 (5.8) × 10^{-8} mol litre^{-1}, respectively). Thus isoproterenol was more potent in non-failing than in failing hearts.

There were no significant differences between the time-matched control groups obtained in non-failing and failing hearts (fig. 1). In both cases, morphine induced cardiac inhibition. In the non-failing heart, morphine significantly reduced ($P < 0.05$; $P < 0.01$; $P < 0.001$) cardiac inhibition at concentrations ranging from 10^{-9} to 10^{-3} mol litre^{-1} compared with

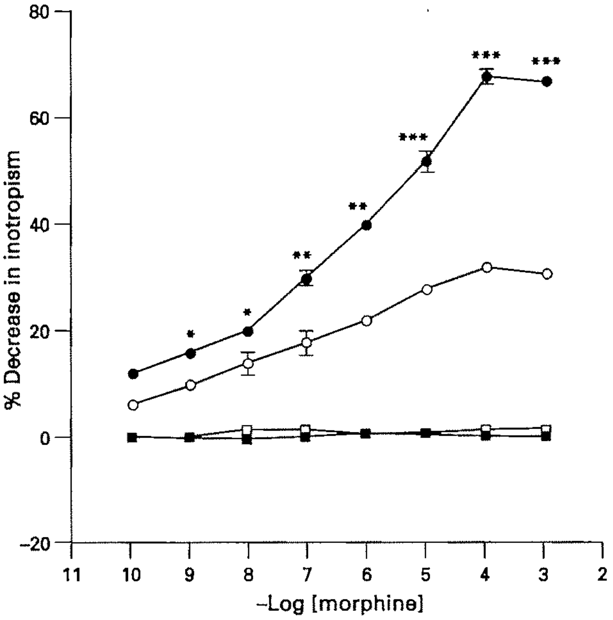


Figure 1 Concentration–response curves for morphine (●, ○) in isolated electrically stimulated human right atrial strips from non-failing (filled symbols) and failing (open symbols) hearts (■, □ = control). Average auricular inotropism (mean (SEM)) for non-failing hearts was 0.90 (0.05) *g* and 0.89 (0.02) *g* for failing hearts. $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ *vs* failing heart. Each point represents the mean (SEM) of eight experiments for each experimental group.

Table 1 Maximal inhibitory effects, IC_{30} and slope for morphine in the absence or presence of naloxone (Nx) in auricular strips of patients without heart failure (mean (SEM)) ($n = 4$–8). Lower and upper = minimum and maximum slopes of the concentration–response curves

Drugs	%Maximum inhibition	$IC_{30} \times 10^{-8}$ mol litre^{-1}	Slope	r	Lower	Upper
Morphine	68 (1.5)	3.9 (0.2)	8.9 (0.7)	0.98	7.1	10.7
Morphine+Nx (10^{-8} mol litre^{-1})	69 (1.2)	4.8 (0.9)	9.2 (0.8)	0.97	7.2	11.2
Morphine+Nx (10^{-7} mol litre^{-1})	67 (1.4)	5.1 (0.8)	9.0 (0.7)	0.98	7.2	10.8
Morphine+Nx (10^{-6} mol litre^{-1})	68 (1.3)	5.6 (1.0)	9.1 (0.7)	0.97	7.2	11.1

Table 2 Maximal inhibitory effects, IC_{30} and slope for morphine in the absence or presence of naloxone (Nx) in auricular strips of patients with heart failure (mean (SEM)) ($n = 4$–8). Lower and upper = minimum and maximum slopes of the concentration–response curves

Drugs	%Maximum inhibition	$IC_{30} \times 10^{-8}$ mol litre^{-1}	Slope	r	Lower	Upper
Morphine	32 (1.0)	5010 (200)	3.9 (0.2)	0.98	3.3	4.5
Morphine+Nx (10^{-8} mol litre^{-1})	33 (0.8)	5600 (250)	3.9 (0.2)	0.99	3.3	4.5
Morphine+Nx (10^{-7} mol litre^{-1})	33 (1.2)	6710 (220)	3.7 (0.2)	0.98	3.1	4.2
Morphine+Nx (10^{-6} mol litre^{-1})	34 (1.8)	6520 (190)	4.3 (0.2)	0.98	3.7	5.0

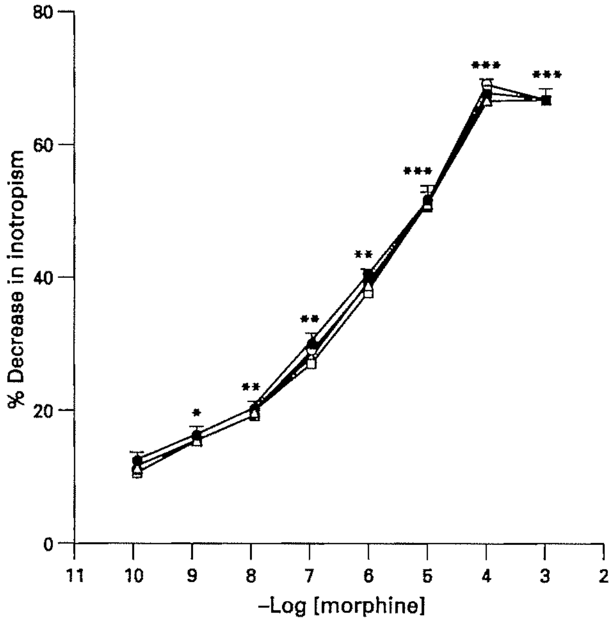


Figure 2 Concentration–response curves for morphine in isolated electrically stimulated human right atrial strips from non-failing hearts in the absence (●, $n = 8$) and presence of naloxone 10^{-8} (○, $n = 4$), 10^{-7} (△, $n = 4$) or 10^{-6} (□, $n = 4$) mol litre^{-1}. Average auricular inotropism (mean (SEM)) in the absence of naloxone was 0.99 (0.05) *g*, and 0.93 (0.05) *g*, 0.96 (0.08) *g* and 0.98 (0.05) *g* in the presence of naloxone 10^{-8}, 10^{-7} and 10^{-6} mol litre^{-1}, respectively. Each point represents mean (SEM). $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ compared with morphine alone.

the time-matched control. However, the inhibition caused by morphine was reduced in failing compared with non-failing hearts (fig. 1). Thus the maximal effect obtained by morphine (32 (1.0) %) was lower ($P < 0.001$) than that obtained in the non-failing heart (68 (1.5) %). Comparison of IC_{30} values (tables 1, 2) indicated that the morphine concentration–response curves were significantly ($P < 0.001$) shifted to the right in preparations from failing hearts (fig. 1). Thus morphine was significantly ($P < 0.001$) more potent in non-failing than in failing hearts (tables 1, 2). As illustrated in tables 1 and 2, the slope of morphine in non-failing hearts was higher ($P < 0.01$) than that obtained in failing hearts.

To determine if the effects of morphine could be attributed to activation of opioid receptors, we studied the action of this drug in the presence of naloxone 10^{-8}, 10^{-7} or 10^{-6} mol litre^{-1} on auricular strips from patients with and without heart failure. In both cases cardiac inhibition induced by morphine was not antagonized (figs 2, 3; tables 1, 2).

Discussion

The high concentrations of morphine used in this study are equivalent to those in patients given morphine for pain relief. Thus high plasma morphine concentrations (> 10^{-6} mol litre^{-1}) occur during the first minute after morphine 10 mg i.v. [13].

It has been shown that morphine, DAMGO, DPDPE and U-50,488H induced cardiac inhibition in rats [1, 14]. Similarly, morphine inhibited auricular inotropism in a concentration-dependent manner in preparations from patients without heart failure. However, the cardiac inhibitory effects of morphine obtained in isolated left atria of the rat were lower than those observed in this study. These differences may represent an intrinsic difference in excitation–contraction coupling between human and rat myocardium.

The negative inotropic effects induced by morphine in both failing and non-failing hearts were not antagonized by naloxone. Although morphine has a higher selectivity for μ receptors, at the concentrations studied it can bind to σ and κ receptors, and

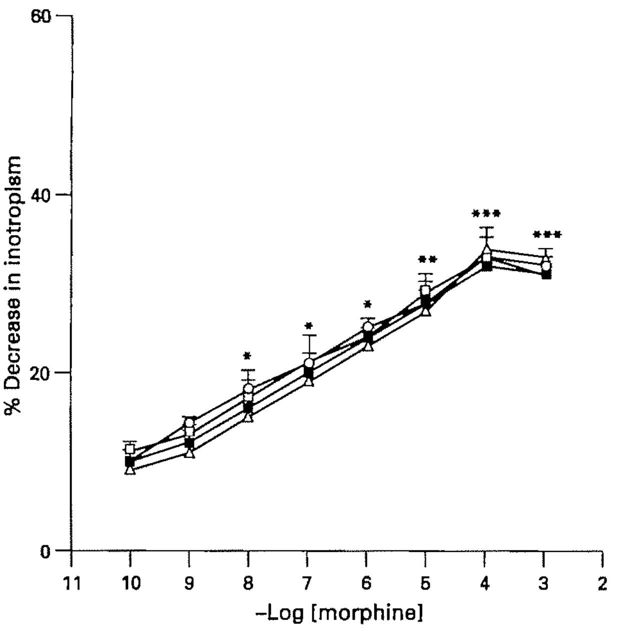


Figure 3 Concentration–response curves for morphine in isolated electrically stimulated human right atrial strips from failing hearts in the absence (■, $n = 8$) and presence of naloxone 10^{-8} (□, $n = 4$), 10^{-7} (○, $n = 4$) or 10^{-6} (△, $n = 4$) mol litre^{-1}. Average auricular inotropism (mean (SEM)) in the absence of naloxone was 0.89 (0.02) *g*, and 0.91 (0.05) *g*, 0.99 (0.03) *g* and 0.99 (0.08) *g* in the presence of naloxone 10^{-8}, 10^{-7} and 10^{-6} mol litre^{-1}, respectively. Each point represents mean (SEM). $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ compared with morphine alone.

therefore in this study we used high concentrations of naloxone to antagonize all three types of opioid receptor [15]. Our data demonstrated that opioid receptors were not involved in the inhibitory effects of morphine. Similarly, other authors [5, 16–18] have described that the cardiac effects induced by high doses or concentrations of opioids are not mediated by opioid receptor activation. If the inhibitory cardiac response induced by morphine was not mediated by opioid receptors, then other mechanisms may be considered. One possibility is that the drug may be interacting with other receptor systems known to mediate inhibitory cardiac effects, such as the muscarinic receptor system; if so the muscarinic antagonist, atropine, should have eliminated this effects. However, previous studies in our laboratory have demonstrated that atropine failed to modify the negative inotropic and chronotropic effects induced by opioid agonists in isolated cardiac tissues [17, 18], thus excluding the involvement of muscarinic receptors.

An earlier investigation [19] demonstrated an interaction between the opioid and adrenergic systems in spontaneously beating guineapig atria. Opioids inhibited the cardiac response to adrenergic stimulation in both atrial and ventricular preparations [20–22]. Therefore, another possible explanation for the inhibitory effects of opioids in these studies is presynaptic inhibition of the sympathetic nervous system. Thus a previous study in our laboratory showed that the negative inotropic effect induced by opioids in left atria of the rat was not apparent in the presence of reserpine [17]. Furthermore, this response to opioid agonists was dependent on β adrenergic mechanisms as it was eliminated by prior block with propranolol [17].

Thus our data and the studies of others described above demonstrate that the negative inotropic action of morphine on the heart is mediated by a non-opioid mechanism and suggest that an adrenergic mechanism may be involved.

We have also demonstrated for the first time that the negative inotropic response to morphine was decreased markedly in heart failure. Thus the concentration–response curve for morphine was shifted to the right and the maximum inhibition to morphine was decreased in failing hearts. Changes in the concentration–response curves for opioid agonists, such as horizontal position, maximum effect and slope, may involve alterations in the affinity of the receptor for the agonist, the density of opioid receptors or the efficacy of the drug–receptor interaction [23]. However, our data clearly demonstrated that the inhibitory cardiac response to morphine was not mediated by opioid receptors, which leads to the conclusion that the decrease in negative inotropic response to opioids in failing hearts could not be explained by changes in the density or affinity of opioid receptors.

It is known that heart failure is characterized by profound β adrenergic receptor desensitization in the myocardium, apparent as depressed inotropic responsiveness to β adrenergic agonists [24, 25], mediated by several disorders in β adrenergic receptor signalling [26, 27]. Abnormal myocardial β adrenergic signal transduction is characterized by selective β_1 receptor downregulation [11, 28, 29]. Our data are in agreement with these studies. Thus the positive inotropic effects induced by isoproterenol were decreased in the failing heart. Moreover, isoproterenol was more potent in the non-failing compared with the failing heart.

Another explanation for the inhibitory cardiac effects of opioids is interaction at the level of the post-receptor transduction cascades. It has been demonstrated that β adrenoceptor-sensitive adenylate cyclase is inhibited by μ opioid agonists in rat striatal neurones [30]. In addition, opioid agonists and antagonists potentiate the cardiac effect of β adrenergic agonists by a mechanism unrelated to the binding of these drugs to opioid receptors [31]. Moreover, propranolol antagonized the pressor effects of [met]enkephalyl Arg^{6}-Phen^{7} in the anaesthetized rat [32] and the excitatory effects of morphine on ventricular automaticity [33] while potentiating the negative chronotropic effects of U-50,488H [20]. In addition, naloxone potentiated the cardiovascular responses to sympathomimetic amines [34]. These studies support the concept that a β adrenergic mechanism could be involved in the cardiac effect of opioids. If an interaction between opioid agonists and β adrenergic receptors were responsible for the negative inotropic response to morphine obtained in our preparations, the decrease in the inhibitory cardiac response to morphine obtained in the failing heart could be explained by selective β_1 adrenoceptor downregulation that occurs in heart failure.

References

1. Laorden ML, Hernández J, Carceles MD, Miralles FS, Puig MM. Interaction between halothane and morphine on isolated heart muscle. *European Journal of Pharmacology* 1990; **175**: 285–290.
2. Valcarcel MI, Ruiz F, Laorden ML. Interaction between morphine and noradrenaline on isolated heart muscle. *General Pharmacology* 1991; **22**: 577–579.
3. Ruiz F, Valcarcel MI, Laorden ML. Temperature-dependent effects of morphine on the isolated right atrium. *Pharmacology* 1992; **44**: 165–168.
4. Nawrath H, Rupp J, Jakob H, Sack U, Mertzlufft F, Dick W. Failure of opioids to affect excitation and contraction in isolated ventricular heart muscle. *Experientia* 1989; **45**: 337–339.
5. Pugsley MK, Pennz WP, Walker MJA, Wong TM. Cardiovascular action of the κ-agonist, U-50,488H, in the absence and presence of opioid receptor blocked. *British Journal of Pharmacology* 1992; **105**: 521–526.
6. Holaday JW. Cardiovascular consequences of endogenous opiate antagonist. *Biochemical Pharmacology* 1983; **32**: 573–583.
7. Liang CS, Imai N, Stone CK, Woolf PD, Kawashima S, Tuttle RR. The role of endogenous opioids in congestive heart failure: effects of nalmefene on systemic and regional hemodynamics in dogs. *Circulation* 1987; **75**: 443–451.
8. Fontana F, Berndi P, Pich E, Capelli M, Bortoluzzi L, Spampinato S, Canossa M. Relationship between plasma atrial natriuretic factor and opioid peptide. *European Heart Journal* 1993; **14**: 219–225.
9. Lowe H. Role of endogenous opioids in heart failure. *Zeitschrift fur Kardiologie* 1991; **8**: 45–71.
10. Daly PA, Sole MJ. Myocardial catecholamines and the pathophysiology of heart failure. *Circulation* 1990; **82**: 135–143.
11. Feldman A. Modulation of adrenergic receptors and G-transduction proteins in failing human ventricular myocardium. *Circulation* 1993; **87**: IV-27–IV-34.
12. Tallarida RJ, Murray RB. *Manual of Pharmacologic Calculations with Computer Programs*. New York: Springer-Verlag, 1987.
13. Sear JW, Hand CW, Moore RA, McQuay HJ. Studies on morphine disposition: Influence of general anaesthesia on plasma concentrations of morphine and its metabolites. *British Journal of Anaesthesia* 1989; **62**: 22–27.
14. Micol JA, Laorden ML. Interaction between halothane and mu, delta and kappa opioid agonists on the isolated right atria of the rat. *British Journal of Anaesthesia* 1992; **69**: 487–491.
15. Von Voigtlander PF, Lahti RA, Luddens JH. U-50,488H: A selective and structurally novel non-mu (kappa) opioid agonist. *Journal of Pharmacology and Experimental Therapeutics* 1983; **224**: 7–12.
16. Pugsley MK, Penz WP, Walker MJA, Wong TM. Antiarrhythmic effects of U-50,488H in rats subject to coronary artery occlusion. *European Journal of Pharmacology* 1992; **212**: 15–19.
17. Micol JA, Laorden ML. Effects of U-50,488H on isolated left atria of the rat. *Pharmacological Communications* 1993; **3**: 63–71.
18. Micol JA, Laorden ML. Effects of μ-, σ- and κ-agonists on isolated right atria of the rat. *Neuropeptides* 1994; **26**: 365–370.
19. Hathorn LF, Caffney JL, Kutsky P, Parker JL. In vitro effects of opiate peptides in guinea pig myocardium. *Circulatory Shock* 1985; **16**: 73–78.
20. Ledda F, Mantelli L, Corti V. Sensitivity to dynorphin-(1-13) of the presynaptic inhibitory opiate receptors of the guinea-pig heart. *European Journal of Pharmacology* 1985; **117**: 377–380.
21. Mantelli K, Corti V, Ledda F. On the presence of opioid receptors in the guinea-pig ventricular tissue. *General Pharmacology* 1987; **18**: 309–311.
22. Ledda F, Corti B, Mantelli L. Indirect evidence for a role of prostaglandins as second messengers of the prejunctional effect of opioids in guinea pig ventricular preparations. *European Journal of Pharmacology* 1989; **162**: 323–327.
23. Johnson SM, Fleming WW. Mechanisms of cellular adaptive sensitivity changes: Applications to opioid tolerance and dependence. *Pharmacological Reviews* 1989; **41**: 435–488.
24. Fowler MB, Laser JA, Hopkins GL, Minobe W, Bristow MR. Assessment of β-adrenergic receptor pathway in the intact failing human heart: progressive receptor down-regulation and subsensitivity to agonist response. *Circulation* 1986; **74**: 1290–1302.
25. Colucci WS, Ribeiro JP, Bocco MB, Quigg RJ, Creager MA, Marsh JD, Gauthier DF, Hartley LH. Impaired chronotropic response to exercise in patients with congestive heart failure. *Circulation* 1989; **80**: 314–323.
26. Brodde OE, Zekowski HR, Doetsch N, Motomura S, Khamssi M, Michel MC. Myocardial beta-adrenoceptor changes in heart failure: concomitant reduction in beta$_1$ and beta$_2$-adrenoceptor function related to the degree of heart failure in patients with mitral valve disease. *Journal of the American College of Cardiology* 1989; **14**: 323–331.
27. Roth DA, Urasawa K, Helmer GA, Hammond HK. Down-regulation of cardiac guanosine 5′-triphosphate-binding proteins in right atrium and left ventricle in pacing-induced congestive heart failure. *Journal of Clinical Investigation* 1993; **91**: 1939–1949.
28. Brown L, Dighton NM, Bals S, Söhlmann W, Zerkowski HR, Michel MC, Brodde OE. Spare receptors for β-adrenoceptor-mediated positive inotropic effects of catecholamines in the human heart. *Journal of Cardiovascular Pharmacology* 1992; **19**: 222–226.
29. Kiuchi K, Sato N, Shannon RP, Vatner DE, Morgan K, Vatner SF. Depressed β-adrenergic receptor- and endothelium-mediated vasodilation in conscious dogs with heart failure. *Circulation Research* 1993; **73**: 1013–1023.
30. Van Vliet BJ, Ruls SR, Drukarch B, Mulder AH, Schoffelmeer ANM. β-adrenoceptor-sensitive adenylate cyclase is inhibited by activation of μ-opioid receptors in rat striatal neurons. *European Journal of Pharmacology* 1991; **195**: 295–297.
31. Kindman LA, Kates RE, Ginsburg R. Opioids potentiate contractile response of rabbit myocardium to the beta adrenergic agonist isoproterenol. *Journal of Cardiovascular Pharmacology* 1991; **17**: 61–67.
32. Douglas H, Kitchen I. Mechanisms involved in the cardiovascular responses to opioid products of proenkephalin in the anaesthetized rat. *General Pharmacology* 1992; **23**: 269–277.
33. Romero H, Laorden ML, Hernández J, Serrano JS. Evidence for involvement of catecholamines in the effect of morphine on ventricular automaticity in the rat. *Journal of Autonomic Pharmacology* 1991; **11**: 93–99.
34. Feria M, Alvarez C, Domínguez J, Sánchez A, Boada J. Naloxone potentiation of cardiovascular responses to sympathomimetic amines in the rat. *Journal of Pharmacology and Experimental Therapeutics* 1992; **255**: 253–258.

British Journal of Anaesthesia 1996; **76**: 111–115

A perfusion system for *in vitro* measurement of human cilia beat frequency†

D. A. SELWYN, A. GYI, J. H. RAPHAEL, A. KEY AND J. A. LANGTON

Summary

We have designed and built a perfusion system and perfusion chamber to allow investigation of the effects of anaesthetic agents on human cilia *in vitro*. Using this system, samples of human respiratory cilia can be maintained in a stable and controlled environment for several hours. We measured cilia beat frequency of nasal respiratory epithelium from 10 healthy volunteers; cilia beat frequency was constant over a 4-h period, and measurements were found to be in good agreement with previously published work [1]. In a separate study we investigated the effect of a sleep dose of propofol on cilia beat frequency in samples from six patients undergoing minor surgery; samples were obtained before and immediately after induction of anaesthesia with propofol 2–3 mg kg^{-1}. There was no statistically significant difference in cilia beat frequency between data obtained before and after induction with propofol. (*Br. J. Anaesth.* 1996; **76**: 111–115)

Key words

Anaesthetics i.v., propofol. Lung, trachea. Equipment, perfusion system.

After routine surgery, impairment of respiratory epithelial cilia function may predispose patients to develop areas of atelectasis and postoperative chest infection; the overall incidence of chest infection after upper abdominal surgery may be as high as 20% [2]. It has been demonstrated that volatile anaesthetic agents cause a decrease in mucus transport rate [3] which is an important host defence mechanism. Respiratory epithelial cilia have a beat cycle which is specialized to facilitate transport of mucus and inhaled particles to the oropharynx, where they may be swallowed or expectorated. Mucus transport rate is dependent on the interrelationship between cilia beat frequency (CBF) and the viscoelastic properties of mucus [4, 5]. A previous pilot study from our laboratory has shown that halothane has a significant depressant effect on CBF [6], but the mechanism of this effect is not known.

In order to study the effects of anaesthetic agents on human respiratory epithelial cilia in a controlled environment, it was necessary to build a new perfusion chamber, as chambers described previously did not satisfy our requirements for the investigation of anaesthetic agents. This new perfusion chamber enabled us to investigate the survival of respiratory cilia *in vitro* and the effect of repeated measurements of CBF.

Materials and methods

PERFUSION CHAMBER

The perfusion chamber was constructed from aluminium in two halves, with an integral perfusion channel that allowed fluid exchange (fig. 1). The cilia sample was placed between a lower fixed cover slip and an upper removable cover slip. The upper cover slip was manufactured specially with a diameter of 45 mm and was sealed using a silicone impregnated rubber washer. It is this large cover slip which allows a wide plane of movement by the microscope objective lens. The chamber depth was 0.85 mm, producing a small internal volume of 1.1 ml.

Cilia beat frequency has been shown to be dependent on temperature [9] and therefore the perfusion system incorporated several features to maintain a constant temperature. The perfusate was kept in a heated water bath maintained at 40 °C. The perfusion channels upstream of the chamber passed through a countercurrent water jacket maintained at 40 °C. The chamber incorporated an integral thermostatically controlled heating element set to 37 °C (fig. 2). The system was calibrated with a thermocouple located in the middle of the external surface of the cover slip and the measured temperature varied by ±0.1 °C. The whole chamber was closed with an annular threaded screw and a composite locking device.

The cilia sample was perfused with Hanks balanced salt solution (HBSS, Gibco, Life Technologies) from an aerated reservoir. This was connected to the chamber using metallic tubing. The medium reservoir was maintained at a height of 25 cm above the microscope stage to allow gravity feed of the medium at a rate of 0.5 ml min^{-1}. A calibrated photometric drip counter enabled a constant flow rate to be maintained.

D. A. SELWYN, MB, BS, FRCA, A. GYI*, MB, BS, FRCA, J. H. RAPHAEL, MB, CHB, FRCA, A. KEY, BSC (HON), J. A. LANGTON, MB, BS, MD, FRCA, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. Accepted for publication: August 25, 1995.

*Present address: Albert Einstein Medical Center, Philadelphia, USA.

†A preliminary account of this work was presented at the Anaesthetic Research Society, Liverpool Meeting, March 25–26, 1994 (*British Journal of Anaesthesia* 1994; 73: 269P).

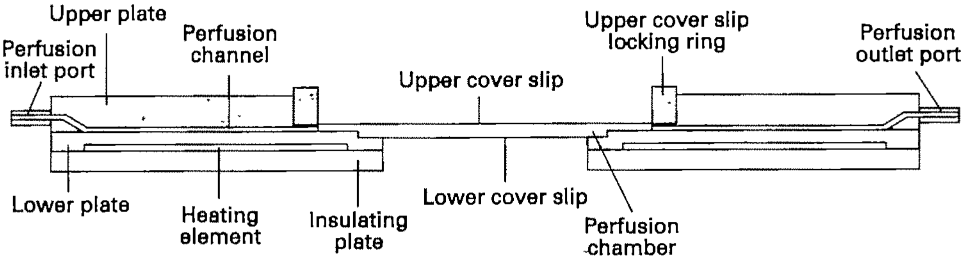


Figure 1 Section through the perfusion chamber.

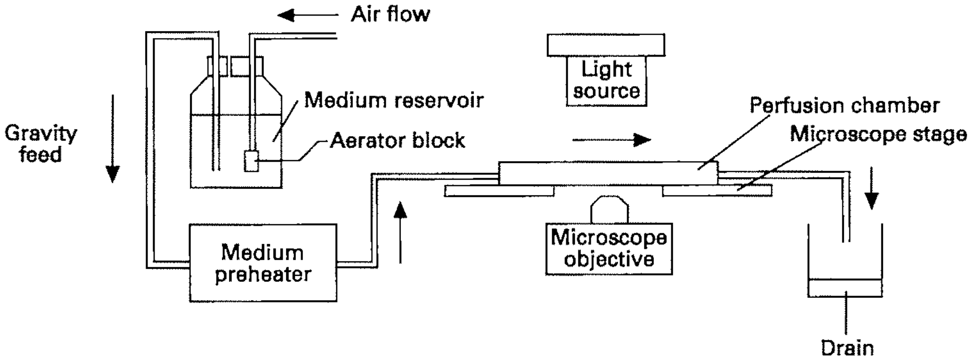


Figure 2 Schematic diagram of the cilia perfusion system.

MEASUREMENT OF CILIA BEAT FREQUENCY

CBF was measured using a television–video modification of the transmitted light technique described originally by Teichtahl, Wright and Kirsner [7]. This technique uses a pinhole photodiode placed against a television image of ciliated epithelium. Movement of the beating cilia across the photodiode produces a characteristic signal which can be viewed on an oscilloscope before a 15-s sample is downloaded to a 386 sx computer (Dell Computer Corporation, Bracknell, UK). Having undergone low-pass filtering (25 Hz) to reduce interference, the signal was sampled at 200 Hz by an analogue to digital converter, stored and displayed. The signal was then processed using mathematica 2.2 software (Wolfram Software, USA) to produce a power spectrum using fast Fourier transforms. CBF was taken as the peak of the power spectrum.

After specimens of cilia were loaded into the perfusion chamber, two readings were obtained from as many edges as possible during a 20-min sampling period, edge selection criteria being those described previously [6]. In summary these comprised: measurements made only from free edges of ciliated epithelium; the edge of the epithelium must not be disrupted and it must be greater than 60 µm in length; the edge must not be contaminated with mucus deposits; and single cells and cell groups partially denuded of cilia were not included.

The samples were viewed under a high resolution (×600) microscope (Nikon Diaphot), using the Normaski polarized light technique. The image obtained from the microscope was transmitted to a high resolution video monitor and recorded onto videotape. CBF was measured at hourly intervals for 4 h.

Table 1 Exclusion criteria for volunteers or patients recruited for measurement of cilia beat frequency

History of asthma, hay fever or atopy.
History of smoking or cessation of smoking within the past 2 yr.
History of upper respiratory tract infection within the preceding month.
History of coagulation or bleeding diathesis.
History of cystic fibrosis, bronchiectasis or documented cilia motility problems.

VALIDATION OF CHAMBER PERFORMANCE

To study the time taken for drug concentrations to change within the chamber and to ensure that flow streaming did not occur, we perfused the chamber with HBSS at a steady rate through a chamber mounted on a light box. Photographs were taken at 30-s intervals from a camera (Pentax UK Limited) at a fixed height (41.5 mm) above the light box using a shutter speed of 1/15 s with an aperture of f11 on to ISO 100 film (Kodak Limited, USA). After a 2-min stabilization period, the perfusate was changed to HBSS containing a known concentration of Dylon ivory black dye. After 5 min the perfusate was changed back to HBSS only. The change in dye colour or wash-in effect was analysed using a densitometer (LKB, Bromma), performing a line density plot at three cuts across the chamber photographs; an inlet cut, a central cut and an outlet cut.

CILIA SURVIVAL EXPERIMENTS

This study was conducted in two parts. In the first part of the study, after obtaining Ethics Committee approval and written informed consent, we recruited 10 healthy volunteers (mean age 28.8 yr). All volunteers satisfied our admission criteria (table 1). Nasal sampling is a relatively painless procedure which does not require local anaesthesia. In all cases the method of sampling was identical and we used a small wire bronchoscopy brush to scrape ciliated epithelium from the inferior nasal turbinate or anterior nasal wall, having previously wetted the sample brush in HBSS. The sample obtained was placed immediately into Hanks nutrient medium at room temperature before being transferred to the perfusion chamber within 1 h.

In the second part of the investigation and after obtaining Ethics Committee approval and written informed consent, we recruited six unpremedicated ASA I patients, undergoing removal of wisdom teeth under general anaesthetic. Nasal sampling, as previously described, was performed immediately before induction of anaesthesia and again after a sleep dose of propofol 2–3 mg kg^{-1}. A separate wire bronchoscopy brush was used for each specimen. The samples obtained were placed into nutrient medium, at room temperature, before being transferred to the perfusion chamber within 1 h.

Baseline CBF measurements were obtained when the specimen had been placed within the chamber, and this represented time point zero. CBF readings were repeated 1 h later. The chambers were perfused with nutrient medium throughout the experiment and maintained at 37 °C (±0.1 °C).

Statistical analysis was performed using SPSS for windows v 5.01 to give analysis of variance for repeated measures using MANOVA (multiple analysis of variance). Statistical significance was taken at $P < 0.05$.

Results

VALIDATION OF THE PERFUSION SYSTEM

The results of the line density studies are shown in figure 3. The densitometer performed a vertical line density plot across the chamber at three points. The change in density of the perfusion dye (mean density, arbitrary units) was plotted against time in seconds. The smooth advancement of the wavefront can be seen in the three areas of study: the inlet of the chamber, the central portion of the chamber and the exit region. The outlet region showed a delayed time course with respect to the inlet region. The time taken for change within the chamber to plateau was approximately 160 s. There was no evidence of flow streaming or any areas of diminished perfusion.

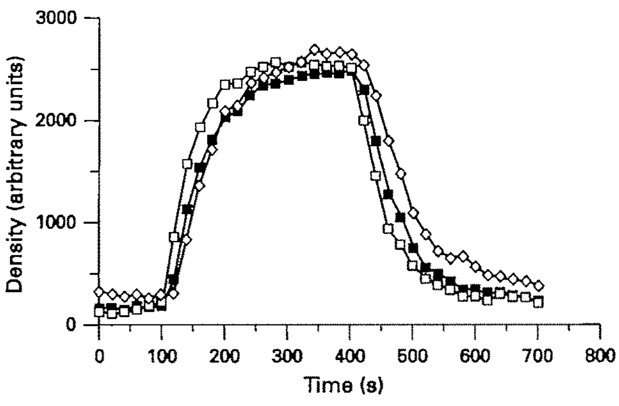


Figure 3 Change in dye concentration with time for the three cuts (inlet (□), middle (■) and outlet (◇) cuts) across the chamber.

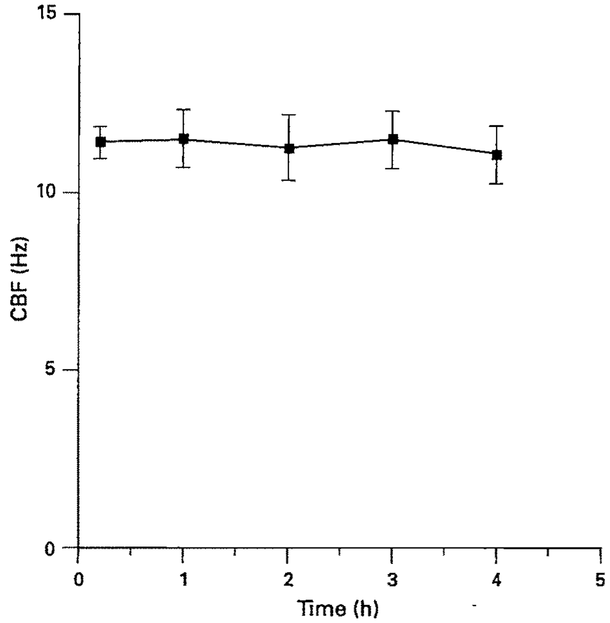


Figure 4 Cilia beat frequency (CBF) *vs* time for volunteer nasal brushings (mean, SD).

Table 2 Beat frequency (mean (SD)) in respiratory epithelial cilia before and 1 h after induction of anaesthesia with propofol

	CBF (Hz) at 1 h	CBF (Hz) at 2 h
Before propofol induction	11.38 (2.33)	11.40 (2.25)
After propofol induction	11.54 (2.17)	11.97 (1.89)

CILIA SURVIVAL EXPERIMENTS

CBF of nasal respiratory epithelium in healthy volunteers is shown in figure 4. The initial readings were taken within 1 h of the specimen being obtained. The subsequent readings were taken at hourly intervals for a total of 4 h. The cilia samples were perfused continuously with Hanks medium. Each reading represents the mean of data from 10 subjects, of which each subject had at least 10 separate readings of CBF at each time. The 15-s sampling period and mean beat frequency represents over 1500 datum points for each subject at each time.

Mean baseline CBF in the volunteer group was 11.3 (SEM 0.774) Hz. The measured CBF was shown to be constant over a 4-h time period and was in good agreement with other published work [1]. There was no statistically significant difference in CBF between the different times.

CBF for patients before and after induction of anaesthesia with propofol is shown in table 2. Time point one represents the baseline readings when the sample had been placed into the chamber and the chamber temperature had stabilized. This was within

60 min of the sample being obtained from the patient. The second time represents CBF measured 1 h later. Mean baseline CBF in the propofol group before induction of anaesthesia was 11.4 (0.93) Hz and after induction 11.7 (0.83) Hz. There was no significant difference between the two groups at each time and CBF was in good agreement with previously published work [1].

There were no anaesthetic complications caused by sampling of nasal respiratory cilia and neither the patients nor the volunteers found the sampling procedure particularly painful.

Discussion

Several factors contribute to mucociliary transport, including mucus quantity and composition, number of ciliated cells, CBF and effectiveness and coordination of cilia beating. The exact relationship between cilia activity or beat frequency and tracheal clearance rate is unclear. A good correlation between CBF and mucus transport rate (MTR) has been reported in some studies [9], whereas in others no direct relationship has been found [10]. Many of the studies investigating CBF have been performed on animal species or have used laboratory apparatus where specimens can be kept for only short periods. Consequently, we designed and validated a perfusion system which allows samples of human respiratory cilia to be kept in a stable and controlled environment for many hours while permitting reliable and repeated measurement of CBF in real time. The chamber design was based on that of Braga [11], with a number of significant improvements; our chamber had a large viewing area to permit increased microscope objective travel across the sample, and it also allowed focusing throughout the whole depth of the sample which improved sample visualization. CBF varies markedly with temperature; increasing temperature from 25 to 37 °C increases CBF by 50 % [12]. Consequently, it is important to have accurate and stable heat control. Our chamber was temperature regulated and maintained a stable sample environment by preheating the perfusate and using an integral thermostatic heating element. The chamber was completely sealed and therefore allowed accurate administration of volatile anaesthetic agents in a known and reliable concentration [13]. Earlier pilot work revealed that volatile agent was lost with plastic tubing, and therefore throughout this system we have used metallic stainless steel tubing to minimize losses.

We have shown that there was uniform flow and therefore perfusion throughout the whole chamber and also that significant flow streaming did not occur. This allowed us to be confident that cilia specimens can be maintained in optimal conditions for long periods of time and that drugs added to the perfusate system will bathe the whole sample under investigation.

We chose a 4-h measurement period to enable us to detect any delayed variation in CBF with time; during this period, cilia maintained normal beat frequencies.

Initial pilot work using a peristaltic perfusion pump produced sample movement and disruption, and was therefore abandoned in favour of a gravity feed system. We chose a perfusion rate of 0.5 ml min^{-1} as it allowed rapid change in chamber conditions without producing sample movement or disruption. Accurate flow of perfusate was ensured by the use of a calibrated photometric drip counter. With the aid of a densitometer, we showed that a change in drug concentration would be expected to equilibrate within the chamber after 160 s. The chamber was easy to assemble, robust and reliable, and easy to clean.

It is known that there are α and β receptors on ciliated epithelium. Studies have shown that autonomic neurotransmitters and neurohormones have a significant influence on mucociliary activity. The action of these neurotransmitters and neurohormones on CBF may be mediated via two different mechanisms, one involving calcium and one via cAMP [14–17]. We found that *in vivo*, after an induction dose of propofol 2–3 mg kg^{-1}, there was no measurable effect on CBF. Halothane has been shown *in vitro* to have a depressant effect on CBF [6] although the mechanism for this is not known, and further work is necessary to elucidate the exact cellular mechanisms involved.

Acknowledgement

This study was supported by an equipment grant from Zeneca Pharma.

References

1. Rutland J, Griffin W, Cole PJ. An in vitro model for studying the effects of pharmacological agents on human cilia beat frequency: effects of lignocaine. *British Journal of Clinical Pharmacology* 1982; 13: 679–683.
2. Dilworth JP, White RJ. Postoperative chest infection after upper abdominal surgery: an important problem for smokers. *Respiratory Medicine* 1992; 86: 205–210.
3. Forbes AR, Gamsu G. Mucociliary clearance in canine lung during and after general anesthesia. *Anesthesiology* 1979; 50: 26–29.
4. Wanner A. Clinical aspects of mucociliary transport. *American Review of Respiratory Disease* 1977; 116: 73–125.
5. Sleigh MA, Blake JR, Liron N. The propulsion of mucus by cilia. *American Review of Respiratory Disease* 1988; 137: 726–741.
6. Gyi A, O'Callahan C, Langton JA. The effect of halothane on cilia beat frequency of ciliated human respiratory epithelium *in vitro*. *British Journal of Anaesthesia* 1994; 73: 507–510.
7. Teichtahl H, Wright PL, Kirsner RLG. Measurement of in vitro ciliary beat frequency: a television–video modification of the transmitted light technique. *Medical and Biological Engineering and Computing* 1986; 24: 193–196.
8. Selwyn DA, Gyi A, Key A, Mottram SD, Langton JA. A perfusion system for the *in vitro* measurement of human cilia beat frequency. *British Journal of Anaesthesia* 1994; 73: 269P.
9. Duchateau GSMJE, Graamans K, Zuidema J, Merkus FWHM. Correlation between nasal cilia beat frequency and mucus transport rate in volunteers. *Laryngoscope* 1985; 95: 854–859.
10. Katz I, Zwas T, Baum GL, Aharonson E, Belfer B. Cilia beat frequency and mucociliary clearance. What is the relationship? *Chest* 1987; 92: 491–493.
11. Braga PC. Versatile perfusion chamber for high-magnification microscopy. *Journal of Pharmacological Methods* 1989; 22: 1–6.

12. Konietzko N, Nakhosteen JA, Mizera W, Kasparek R, Hesse H. Cilia beat frequency of biopsy samples taken from normal persons and patients with various lung diseases. *Chest* 1981; **80**: 855–857.
13. Raphael JH, Selwyn DA, Mottram SD, Langton JA, O'Callaghan C. Effects of 3 MAC of halothane, enflurane and isoflurane on the cilia beat frequency of human nasal epithelium *in vitro*. *British Journal of Anaesthesia* 1996; **76**: 116–121.
14. Robson DAM, Smallman LA, Drake-Lee AB. Factors affecting cilia function in vitro: a preliminary study. *Clinical Otolaryngology* 1992; **17**: 125–129.
15. Sanderson MJ, Dirksen ER. Mechanosensitive and beta-adrenergic control of the cilia beat frequency of mammalian respiratory tract cells in culture. *American Review of Respiratory Disease* 1989; **139**: 432–440.
16. Weiss T, Ghebert L, Shoshan-Barmatz V, Priel Z. Possible mechanism of cilia stimulation by extracellular ATP: involvement of calcium-dependent potassium channels and exogenous Ca^{2+}. *Journal of Membrane Biology* 1992; **127**: 185–193.
17. Lansley AB, Sanderson MJ, Dirksen ER. Control of the beat cycle of respiratory tract cilia by Ca^{2+} and cAMP. *American Journal of Physiology* 1992; **263**: L232–L242.

British Journal of Anaesthesia 1996; **76**: 116–121

Effects of 3 MAC of halothane, enflurane and isoflurane on cilia beat frequency of human nasal epithelium *in vitro*

J. H. RAPHAEL, D. A. SELWYN, S. D. MOTTRAM, J. A. LANGTON AND C. O'CALLAGHAN

Summary

We have measured the effects of three times the minimum alveolar concentration (MAC) of halothane, enflurane and isoflurane on cilia beat frequency of human nasal epithelial brushings from 18 healthy adult patients. Using the transmitted light technique and paired perfusion chambers, the cilia were exposed to 2.25% halothane, 5% enflurane or 3.6% isoflurane in air, or air alone, in a controlled and blinded manner. Over a 4-h observation period, cilia beat frequency of the samples exposed to inhalation anaesthetic agents demonstrated a significant reduction in frequency compared with controls exposed to air alone. Mean cilia beat frequency for the samples exposed to halothane was 9.3 (SEM 1.3) compared with its controls of 11.4 (1.0); for the samples exposed to enflurane, 10.9 (1.3) compared with its controls of 11.6 (1.2); and for the samples exposed to isoflurane, 10.8 (1.1) compared with its controls of 11.6 (1.2). There was a statistically significant difference between the samples exposed to all three volatile agents and their associated controls (halothane, $P = 0.01$; enflurane, $P = 0.03$; isoflurane, $P = 0.01$; nested repeated measures analysis of variance utilizing polynomial contrasts). (*Br. J. Anaesth.* 1996; **76**: 116–121)

Key words

Anaesthetics volatile, halothane. Anaesthetics volatile, enflurane. Anaesthetics volatile, isoflurane. Lung, trachea.

Respiratory infections are a major cause of morbidity after surgery and are particularly common following upper abdominal surgery and in smokers [1]. Despite different anaesthetic techniques, the incidence of postoperative chest infections has remained unchanged over the last 50 yr, ranging from 14 to 21 % for upper abdominal surgery [1–4]. A recent study also demonstrated an increase in mean hospital stay from 7.8 to 10.7 days in those patients developing a postoperative chest infection [1].

There is a predisposition to development of postoperative chest infections in atelectatic regions of the lung where secretions are retained [5]. In clinical practice most emphasis has been placed on promoting mucus clearance by encouraging coughing through improved analgesic regimens; however, the most important natural defence against chest infection is the mucociliary transport system.

Mucus transport depends on the volume and physical properties of the mucus and on the function of the beating cilia. The depressant effects of anaesthetic agents on mucus transport are well established [6–8]; however, the effects of anaesthetic agents on ciliary function have received little attention. In a pilot study, we have recently documented the depressant effect of halothane on human respiratory cilia beat frequency [9].

We have developed a system to expose human ciliated tissue to known concentrations of volatile anaesthetic agents and measure cilia beat frequency in a controlled and blinded manner [10]. With this system we have investigated the effects of 3 MAC of halothane, enflurane and isoflurane on human respiratory cilia beat frequency.

Patients and methods

After obtaining Ethics Committee approval and informed patient consent, we obtained samples of ciliated epithelium from 18 non-smoking healthy patients, eight male, mean age 34.3 (range 22–78) yr, who were not receiving any medications and had not suffered an upper respiratory tract infection within the previous 4 weeks. The patients were unpremedicated.

In a separate study we demonstrated that a single induction dose of propofol had no effect on cilia beat frequency measured subsequently *in vitro* [10]. After an induction dose of propofol 2–3.3 mg kg^{-1}, samples of ciliated respiratory epithelium were obtained by passing a bronchoscopy brush over the inferior nasal turbinates. The brush was agitated in Hanks buffered salt solution (HBSS) to remove the tissue from the brush.

To investigate the effects of the volatile anaesthetic agents on the cilia we designed and built a perfusion system [10]. This comprised two perfusion chambers to house the ciliated tissue from one individual, each consisting of an aluminium block with integral channels at two sides and with reversibly sealed coverslips at the top and bottom. Each chamber was perfused using metallic connecting tubing passing from a separate delivery bottle of HBSS into the

---

J. H. RAPHAEL, FRCA, D. A. SELWYN, FRCA, S. D. MOTTRAM, BSC, J. A. LANGTON, MD, FRCA (University Department of Anaesthesia); C. O'CALLAGHAN, BMEDSCI, MRCP, DM (University Department of Child Health); Leicester Royal Infirmary, Leicester LE1 5WW. Accepted for publication: August 25, 1995.

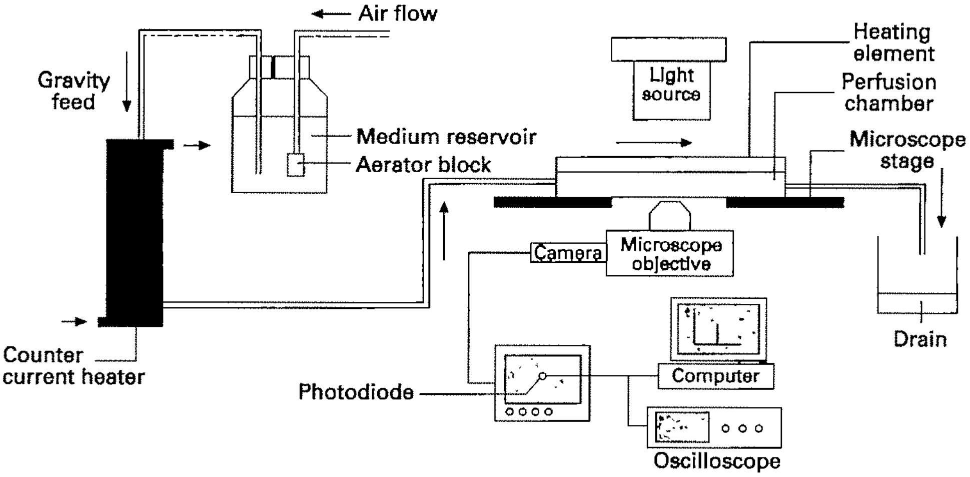


Figure 1 Perfusion system for the *in vitro* measurement of cilia beat frequency.

entry port of the chamber and out from its exit port through plastic connecting tubing into a collecting beaker. The chambers were perfused with HBSS under the effect of gravity at 0.5 ml min^{-1}. Air 1000 ml min^{-1} was either passed directly into one of the bottles of HBSS or passed through a Tec 3 vaporizer before passing into the other bottle. This divergence was achieved in a manner by which the observer was blinded as both metallic delivery tubes were wound around one another within a counter-current water jacket. The outputs from the three Tec 3 vaporizers for halothane, enflurane and isoflurane with an air flow of 1 litre min^{-1} were calibrated using an analyser (Capnomac, Datex).

The bottles of HBSS were immersed in a water bath at 37 °C that also flowed through the counter-current heat exchanger surrounding the metallic delivery tubing. The perfusion chambers were heated to 37 ($\pm$0.1) °C by means of a thermostatically controlled heating element mounted on the underside of the chamber (fig. 1).

To confirm the ability of the system to successfully deliver volatile agents to the chamber, we used halothane as a test agent. We set a calibrated Fluotec 3 vaporizer to 4% and allowed 15 min for equilibration. We sampled the perfusate from the reservoir bottle by aspirating with airtight syringes and obtained samples downstream of the perfusion chamber by attaching the syringes to a T-piece. The samples were extracted into known quantities of n-heptane. These samples were then analysed by gas chromatography (Perkins Elmer 8410) with a DB-17 column, using helium as the carrier gas and detection by flame ionization standardized for halothane [11].

Analysis of cilia beat frequency was performed using a modification of the transmitted light technique that most closely resembles that described previously by Teichtahl, Wright and Kirsner [12]. This method detects ciliary movement by their interference with a light beam which is transduced from the voltage changes of a photodiode and processed mathematically to give a power spectrum of the frequencies produced by ciliary beating. Samples of ciliated epithelium from a patient were mounted between the coverslips of two paired chambers. These were connected to the bottles containing the HBSS perfusate with one bottle receiving the volatile agent in air and the other air alone. When the chambers had equilibrated to 37 °C as indicated by the temperature plate on the chamber base, measurements of cilia beat frequency were commenced. Acceptable ciliated edges for measurement were defined as those devoid of mucus and at least 60 µm long. Measurements were not taken from individual cells or disrupted edges.

Six patient samples were exposed to each of the volatile agents studied and readings were taken from both chambers before exposure to the volatile agent and then at 1, 2 and 3 h after one chamber was exposed to the volatile agent and the other continued to be exposed to air alone. The vaporizer was set at a concentration of 3 MAC for unpremedicated young adults at 37 °C. This represented 2.25% for halothane, 5% for enflurane and 3.6% for isoflurane. We analysed as many acceptable ciliated edges as possible from a minimum of six to a maximum of 10 from each chamber in each defined time band.

STATISTICAL ANALYSIS

The mean of the peak cilia beat frequencies from the power spectrum was computed for each sample at each time. The nested data were analysed by repeated measures analysis of variance (SPSS for windows v5.01). As the effects of volatile agents over time on cilia beat frequency are unknown, we used polynomial contrasts. Significance was taken at $P < 0.05$.

Results

HALOTHANE GAS CHROMATOGRAPHY

Measurements from the gas chromatograph indicated that there was no significant loss of the test volatile agent during perfusion through the system (table 1). From the measured aqueous concentrations of halothane in the delivery bottle and downstream of the perfusion chamber, the equivalent concentrations (in % atm) were calculated and the estimated delivered concentrations were derived from a standard curve and were equivalent to 3.62% (95% confidence intervals (CI) 3.02 to 4.22) for the

Table 1 Mean (SEM) halothane concentrations in the delivery bottle and downstream of the perfusion chamber during exposure to 4% halothane

	Delivery bottle ($n = 4$)	Downstream of chamber ($n = 7$)
Aqueous concn (μmol litre^{-1})	785 (56.2)	933.4 (120.5)
Equivalent concn (% atm)	2.79 (0.2)	3.32 (0.43)
Estimated delivered concn (% atm)	3.62 (0.3)	4.3 (0.55)

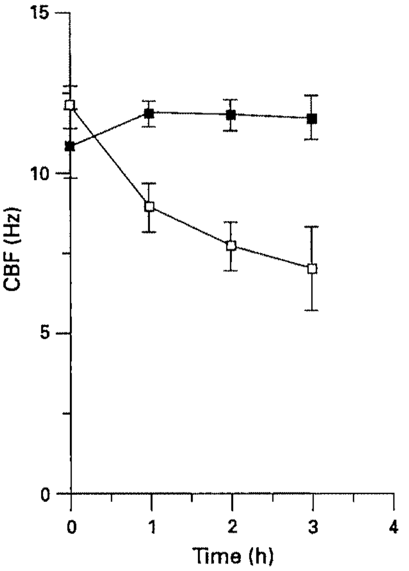


Figure 2 Mean (SEM) nasal cilia beat frequency (CBF) after exposure to 3 MAC of halothane (□) or air (■) for 3 h.

delivery bottle samples and 4.3% (95% CI 3.2 to 5.4) for the samples downstream of the perfusion chamber.

HALOTHANE

There were a total of 349 measurements of cilia beat frequency from the six paired samples exposed to halothane and observed over a 4-h period. Over the 3-h observation period when the cilia were exposed to halothane, mean cilia beat frequency in the group exposed to 3 MAC of halothane in air was 9.3 (SEM 1.3) compared with 11.4 (1.0) in the group exposed to air alone. There was a statistically significant difference between the groups exposed to halothane or air (univariate F test, $F = 9.76$, $P = 0.011$) (fig. 2). The variances at each time for the two treatment groups were not significantly different (Levene's test for equality of variances).

Multiple t tests with Bonferroni correction showed a significant difference between the treatment groups after exposure to halothane for 1, 2 and 3 h (time 0, $P = 1.46$; time 1, $P = 0.028$; time 2, $P = 0.004$; time 3, $P = 0.036$).

ENFLURANE

There were a total of 438 measurements of cilia beat frequency from the six paired samples exposed to enflurane and observed over a 4-h period. Over the 3-h observation period when the cilia were exposed to enflurane, mean cilia beat frequency in the group exposed to 3 MAC of enflurane in air was 10.9 (1.3) compared with 11.6 (1.2) in the group exposed to air alone. The univariate F test was not significant ($F = 2.3$, $P = 0.10$); however, polynomial contrasts were significant for the second polynomial ($F = 6.2$, $P = 0.03$). Thus there was a statistically significant difference between the group exposed to enflurane and the group exposed to air (fig. 3).

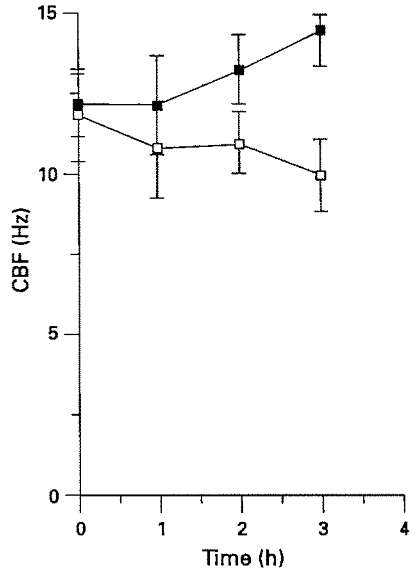


Figure 3 Mean (SEM) nasal cilia beat frequency (CBF) after exposure to 3 MAC of enflurane (□) or air (■) for 3 h.

ISOFLURANE

There were a total of 402 measurements of cilia beat frequency from the six paired samples exposed to isoflurane and observed over a 4-h period. Over the 3-h observation period when the cilia were exposed to isoflurane, mean cilia beat frequency in the group exposed to 3 MAC of isoflurane in air was 10.8 (1.1) compared with 11.6 (1.2) in the group exposed to air alone. The univariate F test was not significant ($F = 3.96$, $P = 0.075$); however, polynomials were significant for the second polynomial ($F = 4.58$, $P = 0.01$). Thus there was a statistically significant difference between the group exposed to isoflurane and the group exposed to air (fig. 4).

Discussion

In this *in vitro* study, we found that 3 MAC of halothane, enflurane and isoflurane significantly reduced cilia beat frequency of human nasal epithelium over a 4-h observation period. There was an unexpected increase in cilia beat frequency in the control group paired with samples exposed to enflurane. The increase in cilia beat frequency in the control group may represent movements of exfoliated collections of cells that became more apparent as the perfusate separated the tissue into smaller segments over time. In our experimental design we controlled for all external factors known to affect cilia beat frequency (temperature, flow rate,

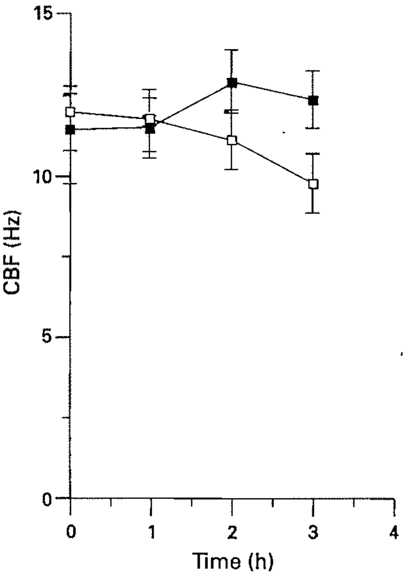


Figure 4 Mean (SEM) nasal cilia beat frequency (CBF) after exposure to 3 MAC of isoflurane (□) or air (■) for 3 h.

pH and osmolality), and when assessing the chamber we found cilia beat frequency to remain stable for many hours [10]. By conducting controlled and blinded experiments we would anticipate that the increase in cilia beat frequency in the control group may have similarly occurred in the paired chamber countered by the depressant effects on cilia beat frequency of the volatile agent.

In this study we used a supraclinical concentration of each volatile agent so as to determine the presence of any effects. This restriction to one concentration makes it impossible to quantitatively compare the agents.

The depressant effects of anaesthetic agents on respiratory mucus clearance are well established [6–8]; however, there has been limited study of the effects of anaesthetics on ciliary function, information relevant to understanding the mechanisms of the depression of mucus transport. The ciliodepressant effects of anaesthetic agents were recognized by Nunn and colleagues 20 yr ago, investigating changes in the swimming velocity of the protozoan, *Tetrahymena pyriformis*, exposed to anaesthetic agents [13]. Manawadu, Mostow and LaForce [14] investigated the effects of halothane on ferret tracheal cilia, but only in a semiquantitative way, by noting the presence or absence of ciliary activity at different sites. Lee and Park demonstrated suppression of cilia beat frequency of rabbit tracheal specimens with halothane and enflurane [15]. They found a 20–25 % reduction in cilia beat frequency with 3 MAC of halothane and enflurane measured after 10 min exposure. This is comparable with the 10 % reduction with enflurane and 25 % reduction with halothane at the earliest time we measured, after exposure for 1 h.

The limited investigations of inhalation anaesthetic agents on cilia beat frequency have been restricted to non-human tissue. Although ciliary structure is similar in different species, ciliary function and in particular mechanisms of control are not uniform. The use of human, rather than non-human, tissue for studying the effects of pharmacological agents in clinical use is therefore preferable. Previous work from our laboratory using a different methodology investigated the effects of halothane on human ciliated tissue [9]. In this study with 1.8 % halothane, there was depression of cilia beat frequency of 25 % after 1 h and 20 % after 2 h exposure and with 5.7 % halothane, reductions of 20 % and 40 % after 1 and 2 h exposure, respectively. These are comparable with our findings of depression of 25 % at 1 h and 40 % after 2 h of exposure to 2.25 % halothane.

The concentration of halothane (measured by gas chromatographic analysis) varied because of loss of some of the agent during sampling as a result of its volatility. The concentration of the volatile agent in the delivery bottle was smaller than downstream of the perfusion chamber, because of the greater difficulties in achieving an airtight seal when sampling from the bottle. The difference in the concentration of halothane in the delivery bottle and downstream of the perfusion chamber was not statistically significant. The derived delivered concentration of halothane downstream of the perfusion chamber with the vaporizer set to 4 % was 4.3 % (95 % CI 3.2 to 5.4) and suggests that this system delivered volatile agents to the ciliated tissue in the sample chamber without significant loss. In an early pilot study, we noted loss of the volatile agent when using plastic connecting tubing and therefore replaced this with metallic tubing.

The ciliated epithelium of the nose sampled in this study has been shown previously to have the same beat frequency as cilia located distally in the bronchial tree [16] and the similarity of our results with those of Lee and Park using rabbit trachea suggests that nasal cells are representative of cilia from more distal parts of the respiratory tract [15]. We have validated our method of sample collection and shown that beat frequency from awake volunteers is the same as that after a sleep dose of propofol [10].

The transmitted light technique for determination of cilia beat frequency first described by Dalmann and Rylander in 1962 is the most widely used method for measurement of cilia beat frequency that is reproducible, convenient to use and requires minimal subjective assessment [17]. We refined Teichtahl's modification [12] by collecting the signals produced by beating cilia over a 15-s period and dividing this into three sequential 5-s intervals for analysis. We computed the peak frequency of one power spectrum obtained by calculating the mean of the power spectra for each epoch. A mean of the dominant frequency of each of the three 5-s epochs was then computed. Although shortening the capture time reduced the resolution of measurement to 0.2 Hz, this was not a limiting factor within the experimental conditions used and it increased the confidence interval of the calculated mean beat frequency.

Postoperative chest infections are a common and serious form of postoperative morbidity and mortality, and a recent study indicated an incidence of 21.5 % after upper abdominal procedures [1]. These infections are associated with smoking [1], vertical surgical incisions [1–4] and prolonged surgery [4].

There is no satisfactory evidence to associate different anaesthetic techniques with the incidence of chest infections. One of the important defences to respiratory infection is mucociliary clearance and this is known to be impaired by some anaesthetic agents [6]; however, the mechanisms involved have not been elucidated. Mucociliary clearance depends on the volume and physical properties of the mucus and the co-ordination and beating frequency of the cilia. It appears that anaesthetic agents may not alter the amount of mucus or its rheological properties [18] and thus it is likely that they alter ciliary function.

We found a 10–25% reduction in cilia beat frequency with these supraclinical concentrations of anaesthetics after 1 h of exposure, yet other workers have demonstrated 80% reduction in the mucus transport rate with similar concentrations of anaesthetic agents [6]. This raises questions about the importance of ciliary beat frequency in determining mucus transport rate.

Forty years ago, Hill investigated the movement of carborundum particles across frog oesophagus and rat trachea [19]. She described a hyperbolic relationship between mucus transport rate and particle velocity such that there were disproportionately larger decreases in mucus transport rates at lower particle velocities. It was hypothesized that this relationship arose because the transfer of power from the beating cilia to the mucus was most effective within a narrow range of ciliary beat frequencies.

Puchelle and Zahm studied the relationship between the transport rate of sputum from bronchitic patients across mucus-depleted frog palate and the rheological properties of sputum [20]. Not surprisingly, the rheological properties of increased viscosity, increased elasticity and reduced spinnability were associated with reduced transport rates; however, the most important determinant of mucus transport rate found by step-by-step multiple regression was ciliary beat frequency.

The exact relationship between cilia beat frequency and the rate of mucus transport is complicated because of the interplay of multiple factors. In a study of 20 patients, Katz and colleagues could not find a direct relationship between cilia beat frequency of human nasal mucosa and tracheal clearance rates using a radioisotope technique. However, in this study the range of mucus transport rates and cilia beat frequencies in the patients studied was small, limiting the chances of finding any relationship if it should exist [21]. Duchateau and co-workers investigated the relationship between nasal cilia beat frequency measured photometrically from biopsies *in vitro* with nasal mucociliary clearance of dye and saccharine *in vivo* in 31 healthy volunteers [22]. The range of mucus transport rates was twice that of Katz's study and a good correlation was found between the logarithm of mucus clearance rate and cilia beat frequency. Hee and Guillerm similarly described a non-linear relationship between cilia beat frequency and mucus transport rates in sheep [23]. These studies suggest that cilia beat frequency may have an important role in determining the transport rate of mucus and that modest reductions in cilia beat frequency may be associated with large reductions in mucus transport rates.

In a separate study [10] we did not find any effect on cilia beat frequency measured 1 h after *in vivo* bolus administration of an induction dose of propofol. This raises the possibility of a difference between this drug and the inhalation agents on respiratory cilia; however, studies of the effects of propofol on cilia beat frequency *in vitro* with on line measurements are required to compare this drug with inhalation agents.

References

1. Dilworth JP, White RJ. Postoperative chest infection after upper abdominal surgery: an important problem for smokers. *Respiratory Medicine* 1992; **86**: 205–210.
2. King DS. Postoperative pulmonary complications. *Surgery Gynecology and Obstetrics* 1933; **56**: 43–50.
3. Wightman JAK. A prospective study of the incidence of postoperative pulmonary complications. *British Journal of Surgery* 1968; **55**: 85–91.
4. Garibaldi RA, Britt MR, Coleman ML, Reading JC, Pace NL. Risk factors for postoperative pneumonia. *American Journal of Medicine* 1981; **70**: 677–680.
5. Gamsu G, Singer MM, Vincent HH, Berry S, Nadel JA. Postoperative impairment of mucus transport in the lung. *American Review of Respiratory Diseases* 1976; **114**: 673–679.
6. Forbes AR. Halothane depresses mucociliary flow in the trachea. *Anesthesiology* 1976; **45**: 59–63.
7. Forbes AR, Horrigan RW. Mucociliary flow in the trachea during anesthesia with enflurane, ether, nitrous oxide and morphine. *Anesthesiology* 1977; **46**: 319–321.
8. Forbes AR, Gamsu G. Mucociliary clearance in the canine lung during and after general anesthesia. *Anesthesiology* 1979; **50**: 26–29.
9. Gyi A, O'Callaghan C, Langton JA. A pilot study of the effect of halothane on human ciliary beat frequency *in vitro*. *British Journal of Anaesthesia* 1993; **71**: 757P–758P.
10. Selwyn DA, Gyi A, Raphael JH, Key A, Langton JA. A perfusion system for the *in vitro* measurement of human cilia beat frequency. *British Journal of Anaesthesia* 1996; **76**: 111–115.
11. Rutledge CO, Siefen E, Alper MH, Flake W. Analysis of halothane in gas and blood by gas chromatography. *Anesthesiology* 1963; **24**: 862–867.
12. Teichtahl H, Wright PL, Kirsner RLG. Measurement of in vitro ciliary beat frequency: a television–video modification of the transmitted light technique. *Medical and Biological Engineering and Computing* 1986; **24**: 193–196.
13. Nunn JF, Sturrock JE, Wills EJ, Richmond JE, McPherson CK. The effect of inhalational anaesthetics on the swimming velocity of *Tetrahymena pyriformis*. *Journal of Cell Science* 1974; **15**: 537–554.
14. Manawadu BR, Mostow SR, LaForce FM. Impairment of tracheal ring ciliary activity by halothane. *Anesthesia and Analgesia* 1979; **58**: 500–504.
15. Lee KS, Park SS. Effect of halothane, enflurane and nitrous oxide on tracheal ciliary activity in vitro. *Anesthesia and Analgesia* 1980; **59**: 426–430.
16. Low P-MP, Luk CK, Dulfano MJ, Finch PJP. Ciliary beat frequency of human respiratory tract by different sampling techniques. *American Review of Respiratory Diseases* 1984; **130**: 497–498.
17. Dalmann T, Rylander R. Frequency ciliary beat measured with a photosensitive cell. *Nature (London)* 1962; **196**: 592–593.
18. Rubin BR, Finegan B, Ramirez O, King M. General anesthesia does not alter the viscoelastic properties of human respiratory mucus. *Chest* 1990; **98**: 101–104.
19. Hill JR. The influence of drugs on ciliary activity. *Journal of Physiology* 1957; **139**: 157–166.
20. Puchelle E, Zahm JM. Influence of rheological properties of

human bronchial secretions on the ciliary beat frequency. *Biorheology* 1984; **21**: 265–272.

21. Katz I, Zwas T, Baum GL, Aharonson E, Belfer B. Ciliary beat frequency and mucociliary clearance: what is the relationship? *Chest* 1987; **92**: 491–493.
22. Duchateau GSMJE, Graamans K, Zuidema J, Merkus FWHM. Correlation between nasal cilia beat frequency and mucus transport rate in volunteers. *Laryngoscope* 1985; **95**: 854–859.
23. Hee J, Guillerm R. Discussion on smoke and mucociliary transport. *European Journal of Respiratory Diseases* 1985; **66** (Suppl. 139): 86–88.

British Journal of Anaesthesia 1996; **76**: 122–129

Effect of phosphodiesterase inhibitors on human arteries *in vitro*

M. B. VROOM, M. PFAFFENDORF, H. B. VAN WEZEL AND P. A. VAN ZWIETEN

Summary

In the present study, we investigated if the relaxant effects of phosphodiesterase (PDE) III inhibitors on human vessels could be inhibited by a nitric oxide synthase blocker, L-NAME, or by a blocker of ATP-sensitive potassium channels (K_{ATP}), glibenclamide. The experiments were performed using an isometric myograph in isolated human s.c. small arteries obtained from healthy donors. After a priming procedure consisting of exposure to high potassium (120 mmol litre^{-1}) solutions, phenylephrine 10 μmol litre^{-1} and an equilibrium period of 30 min, the preparations were contracted with a thromboxane A_2 mimetic agent, U46619 1 μmol litre^{-1}. Subsequently, cumulative concentration–response curves were constructed for the selective PDE III inhibitors amrinone, milrinone and enoximone, and for theophylline and dipyridamole, with and without the addition of L-NAME 100 μmol litre^{-1} or glibenclamide 1 μmol litre^{-1}. Addition of L-NAME to the organ bath resulted in significantly higher pEC_{50} values (−log of the concentration required for 50% relaxation) for milrinone compared with the control: 2.77 (SEM 0.24) mol litre^{-1} ($n = 5$) *vs* 3.49 (0.17) mol litre^{-1} ($n = 7$) ($P < 0.05$). There was no significant difference between any other group. From our data we conclude that the relaxant properties of amrinone, enoximone, theophylline and dipyridamole are not dependent on nitric oxide release or on interaction with K_{ATP} channels. However, the effect of milrinone may be partly endothelium-dependent in human vessels *in vitro*. (*Br. J. Anaesth.* 1996; **76**: 122–129)

Key words

Pharmacology, phosphodiesterase inhibitors. Pharmacology, nitric oxide. Pharmacology, glibenclamide. Arteries, relaxation.

Since the discovery of cyclic nucleotide phosphodiesterase (PDE) activity 30 yr ago, there have been major advances in knowledge on this group of enzymes [1]. Five families have been described, each composed of several isoforms with different patterns of tissue distribution, including cardiac muscle, vascular smooth muscle and platelets [2, 3]. Subsequently, selective isoenzyme inhibitors have been developed [4]. Theoretically, these agents may prove useful in a variety of clinical disorders, including heart failure, asthma, depression or dementia, or arterial thrombosis. None the less, their current use in clinical practice is still limited [5].

Over the past decade, interest has focused on the selective inhibitors of the cardiac PDE peak III isoenzyme for the treatment of congestive heart failure, but the effects of chronic oral administration of these inotropic agents in this condition have been disappointing [6–8]. However, they continue to be used in the treatment of acute heart failure [9, 10]. One of the disadvantages of the currently available PDE III inhibitors, such as amrinone, milrinone and enoximone, is marked vasodilator activity at higher doses, with concomitant reductions in arterial pressure.

The precise mechanism of this vasodilator activity remains to be elucidated. There is little doubt that selective inhibition of a low K_m cAMP PDE, documented in both human arteries and arteries of different animal species, plays a major role [11–15]. In addition, several PDE inhibitors have been shown to produce endothelium-dependent vasodilatation in animal studies [16–18]. Recently, there has been mounting interest in the role of the ATP-dependent potassium (K_{ATP}) channels in cardiovascular tissue. Opening of these K_{ATP} channels may result not only in vasodilatation, but also in marked cardioprotective anti-ischaemic effects [19, 20].

In the present study, we investigated if the vasodilator effects of the PDE III inhibitors amrinone and milrinone, both bipyridines, the imidazolone derivative, enoximone, and the non-specific PDE inhibitors, theophylline and dipyridamole, could be modulated by a nitric oxide synthase blocker, N^G-nitro-L-arginine methyl ester hydrochloride (L-NAME) or by the K_{ATP} channel blocker, glibenclamide. The experiments were performed in isolated human s.c. small arteries, obtained from healthy donors.

Materials and methods

VESSEL DONORS

S.c. arteries were obtained from 11 healthy white female patients (aged 18–49 yr) undergoing reconstructive breast surgery. The study was approved by the hospital's medical Ethics Committee and all patients gave informed consent. The patients were free from cardiovascular disorders and were not

---

M. B. VROOM, MD, H. B. VAN WEZEL, MD, PHD (Department of Anaesthesiology); M. PFAFFENDORF, PHD, P. A. VAN ZWIETEN, MD, PHD (Departments of Pharmacotherapy and Cardiology); Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, Netherlands. Accepted for publication: August 19, 1995.

Correspondence to M.B.V.

receiving any chronic drug treatments, except for oral contraceptive agents. Surgery was performed under general anaesthesia with volatile anaesthetics, supplemented with fentanyl and vecuronium.

PREPARATION AND MOUNTING OF THE VESSELS

Small arteries were dissected atraumatically, immediately after removal of a skin segment with s.c. fat from the caudal segment of the patient's breast. After dissection, a 40-µm diameter stainless steel wire was inserted into the lumen. The length of the vessels was determined using an OSM-4 10×/13 ocular lens (Olympus, Japan). Subsequently, the vessels (estimated length of 1–2 mm) were placed in an organ preservation solution (University of Wisconsin (UW)) [21] and stored at 4 °C for a maximum of 7 days. Before the experiment, the preparations were transferred to the chamber of an isometric myograph [22]. The wire was fixed at both ends to microscrews and a second wire was inserted, which was subsequently connected to a force transducer (Kistler Morse, DSG 6, Redmond, WA, USA). This enabled continuous measurement of the isometric wall tension of the vessel. Reproducible measurements could be obtained within at least 7 h.

The preparations were suspended in Tyrode's solution for 10 min at 37 °C. Throughout the experiment, the buffer solution was oxygenated with carbogen (95% oxygen, 5% carbon dioxide) to achieve a pH of 7.4. Subsequently, the ratio between passive wall tension and internal circumference was determined by a normalization procedure, as described by Mulvany and Halpern [23]. The internal circumference was adjusted to a value that equals 90% of the circumference generated by a transmural pressure of 100 mm Hg (13.3 kPa). This value was then divided by π to obtain the normalized lumen diameter. Mechanical responses were expressed as active tension, δT (N m^{-1}), that is the developed active force divided by twice the vessel segment length.

At the beginning of each experiment, the preparations were contracted three times for 5 min with high potassium Tyrode's solution (K^+ 120 mmol litre^{-1}, see below) and once with phenylephrine 10 µmol litre^{-1}, an α_1 adrenoceptor agonist, at intervals of 15 min. Between these episodes the chambers were flushed at least three times with Tyrode's solution. This episode was followed by an equilibrium period of 30 min for the L-NAME and control groups and 60 min for the glibenclamide group. L-NAME 100 µmol litre^{-1} or glibenclamide 1 µmol litre^{-1} was added at the beginning of this period and remained present in the bath thereafter. An equilibrium period of 60 min was chosen for glibenclamide as this drug has a slow onset of action. Subsequently, U46619, a thromboxane A_2 mimetic agent, was administered to all preparations at a concentration of 1 µmol litre^{-1}. After stabilization of the contraction, a cumulative concentration–response curve, using concentrations of 0.1 µmol litre^{-1} to 1 mmol litre^{-1}, was constructed for amrinone, milrinone, enoximinone, theophylline and dipyridamole.

Our experimental model included two separate force transducers connected to one single organ bath, which enabled simultaneous evaluation of the contractile responses of two vessels to one drug combination. Therefore, the experiments described were performed in duplicate if sufficient vessels could be harvested from the patient's breast. The data of these duplicate experiments were averaged and listed in the results section for each individual patient.

To evaluate the effects of the preservation technique on endothelial function, the response of contracted arteries to methacholine 10^{-5} mol litre^{-1} was determined immediately after dissection of the blood vessel and after preservation in UW fluid. These vessels were not used in any other experiment.

SOLUTIONS AND DRUGS USED

In all experiments, Tyrode's solution of the following composition was used (mmol litre^{-1}): NaCl 136; $NaHCO_3$ 11.9; NaH_2PO_4 0.42; KCl 2.5; $CaCl_2$ 1.8; $MgCl_2$ 0.5; and glucose 5.5. In the high potassium Tyrode's solution, NaCl 117.5 mmol litre^{-1} was replaced by KCl, resulting in a total potassium concentration of 120 mmol litre^{-1}. These solutions were prepared just before each experiment. Aliquots of 20 ml were kept at 37 °C and bubbled with carbogen before they were introduced into the bath.

Amrinone and milrinone (donated by Sanofi Winthrop, Dev. Centre, Fawdon, UK) and enoximone (donated by Marion Merrell Dow Inc., Cincinatti, OH, USA) were dissolved to a concentration of 10^{-1} mol litre^{-1}. Milrinone was dissolved in distilled H_2O, amrinone and enoximone were dissolved in 99% dimethylsulphoxide (DMSO). Subsequently, these agents were diluted to 10^{-2}–10^{-5} mol litre^{-1} in distilled water (amrinone and milrinone) or 66.7% DMSO (enoximone).

Theophylline and dipyridamole (Sigma Chemical Co., USA) were dissolved in distilled water and 66.7% DMSO, respectively, and subsequently diluted to 10^{-2}–10^{-5} mol litre^{-1} in distilled water. The final concentrations ($<1\%$) of DMSO in the bathing medium had no significant effect on vascular smooth muscle contraction and relaxation. (See fig. 1 for the chemical structures of the various compounds studied.)

Nitro-L-arginine methyl ester hydrochloride (L-NAME) (Sigma), U46619 (9,11-dideoxy-11α,9α-epoxy methanoprostaglandin F2α) (Sigma) and L-phenylephrine hydrochloride (Sigma) were dissolved in distilled water. Glibenclamide (Hoechst) was dissolved in 66.7% DMSO.

DATA ANALYSIS

A log concentration–response curve was fitted to the data of individual experiments using GraphPad software (GraphPad, Institute for Scientific Information, San Diego, CA, USA). This computer program allows calculation of the EC_{50} by non-linear regression analysis, which is the concentration of the compound required to achieve the half maximal relaxant effect, based on the equation: E =

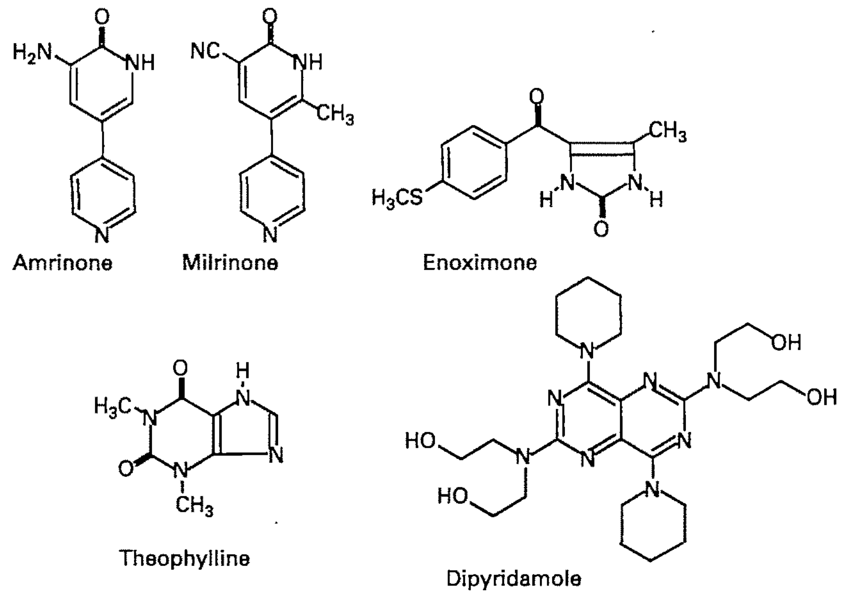


Figure 1 Chemical structures of the various compounds studied.

Emax × $A^P/(A^P + EC_{50}{}^P)$, where E = the response obtained with a given concentration A; the exponent P describes the slope of the relationship (Hill coefficient); and Emax = the maximally obtainable effect.

All data are presented as mean (SEM). Differences between means were compared using a two-tailed Student's t test for unpaired data or analysis of variance where appropriate (Graphpad Instat). $P < 0.05$ was considered significant.

Results

The resistance arteries dissected from the mammary tissues and used to evaluate the effects of the PDE III inhibitors ($n = 116$) had an average diameter of 415 (20) µm and a length of 1.8 (0.03) mm. There were no significant differences in main vessel characteristics between the groups (table 1).

All arteries showed spontaneous rhythmic activity under the experimental conditions. The preparations remained stable and fully responsive to methacholine for at least 1 week after preparation when stored in the UW solution. Maximal relaxation to methacholine 10^{-5} mol litre^{-1} was 97.5 (1.5)% ($n = 4$) on day 0 *vs* 97.3 (1.8)% ($n = 4$) on day 7 (ns). Preservation UW fluid had no influence on the contractile response to U46619 1 µmol litre^{-1}, as linear regression analysis revealed no time-dependent change (correlation coefficient $r = 0.159$, slope not significantly different from zero) (fig. 2). In addition, the contractile responses to phenylephrine remained stable with time: 3.92 (0.32) N m^{-1} ($n = 22$) on day 0 *vs* 5.05 (1.62) ($n = 4$) (ns) on day 7.

All PDE inhibitors induced concentration-dependent vasodilatation in the isolated arteries. Dipyridamole was the most potent vasodilator in our study (pEC_{50} 4.67 (0.22) mol litre^{-1}) and theophylline the least active (pEC_{50} 2.72 (0.07) mol litre^{-1}). The pEC_{50} values for amrinone, milrinone and enoximone were similar in the control groups: 3.28 (0.01), 3.49 (0.17) and 3.29 (0.08) mol litre^{-1}, respectively.

Compared with potassium and phenylephrine, U46619 proved to be the most potent vasoconstrictor

Table 1 Characteristics of the human vessels used in this study (mean (SEM)). L-NAME = N^G-nitro-L-arginine methyl ester

	Age (days)	Length (mm)	Circumference (µm)
Amrinone	3.7 (1.5)	1.8 (0.1)	482 (80)
+ L-NAME	3.8 (1.3)	2.0 (0.0)	338 (102)
+ Glibenclamide	2.1 (0.4)	1.9 (0.1)	419 (57)
Milrinone	4.0 (1.4)	1.8 (0.1)	403 (59)
+ L-NAME	3.8 (1.8)	1.9 (0.1)	385 (96)
+ Glibenclamide	2.5 (0.6)	2.0 (0.0)	383 (61)
Enoximone	3.1 (0.9)	1.9 (0.1)	434 (79)
+ L-NAME	4.0 (1.5)	2.0 (0.0)	479 (125)
+ Glibenclamide	2.1 (0.5)	1.8 (0.2)	336 (51)
Theophylline	3.0 (0.9)	2.0 (0.0)	377 (58)
+ L-NAME	2.6 (1.2)	1.6 (0.2)	259 (50)
+ Glibenclamide	2.3 (1.0)	1.6 (0.2)	357 (65)
Dipyridamole	3.4 (1.6)	1.5 (0.1)	287 (43)
+ L-NAME	3.8 (1.5)	1.9 (0.1)	305 (68)
+ Glibenclamide	3.8 (1.5)	1.9 (0.1)	337 (57)

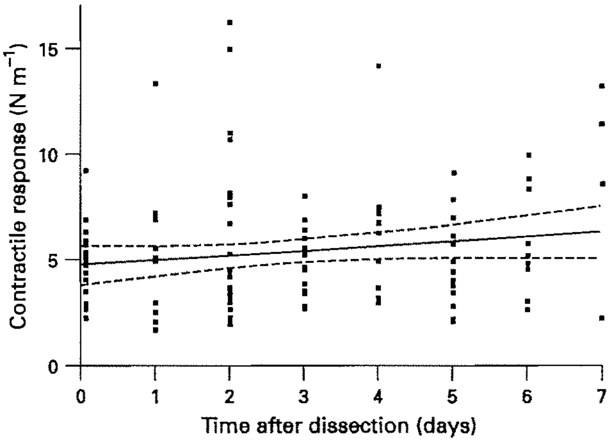


Figure 2 Linear regression analysis of the contractile response to U46619 1 µmol litre^{-1} with respect to days of vessel preservation.

Table 2 Contractile response to U46619 1 µmol $litre^{-1}$ (N m^{-1}) in small human isolated vessels (mean (SEM)); influence of N^G-nitro-L-arginine methyl ester (L-NAME) and glibenclamide

	Control		L-NAME		Glibenclamide	
	No. individuals studied	Force	No. individuals studied	Force	No. individuals studied	Force
Amrinone	6	5.44 (1.64)	5	4.76 (0.75)	6	3.68 (0.67)
Milrinone	7	6.06 (1.54)	5	4.49 (0.70)	6	5.64 (1.24)
Enoximone	6	5.65 (1.77)	5	6.84 (1.21)	6	4.66 (0.98)
Theophylline	5	5.71 (0.65)	5	4.07 (0.64)	8	4.20 (0.68)
Dipyridamole	5	4.03 (2.11)	5	4.31 (1.65)	5	3.95 (1.38)

Table 3 Contractile response (N m^{-1}) to the fourth potassium administration (K^+) and to phenylephrine 10 µmol $litre^{-1}$ (Phe) in small human isolated vessels (mean (SEM)). L-NAME = N^G-nitro-L-arginine methyl ester

	Control		L-NAME		Glibenclamide	
	K^+	Phe	K^+	Phe	K^+	Phe
Amrinone	4.78 (1.55)	4.03 (1.46)	4.17 (0.71)	3.15 (0.58)	4.12 (0.94)	3.69 (0.82)
Milrinone	5.66 (1.34)	4.94 (1.31)	3.71 (0.60)	3.18 (0.51)	5.40 (1.11)	5.02 (1.03)
Enoximone	5.00 (1.67)	4.16 (1.49)	5.76 (0.92)	4.65 (0.65)	4.20 (0.87)	3.63 (0.75)
Theophylline	4.81 (0.69)	4.86 (0.50)	3.45 (0.68)	2.84 (0.67)	4.00 (0.66)	3.52 (0.58)
Dipyridamole	4.39 (0.43)	4.03 (0.38)	4.15 (1.33)	3.63 (1.24)	4.01 (1.01)	3.70 (0.90)

Table 4 pEC_{50} values of the phosphodiesterase inhibitors with respect to the vasodilatation induced by various inhibitors in precontracted small human arteries (mean (SEM)). pEC_{50} = log of the concentration of the compound required to achieve the half maximal relaxation effect; L-NAME = N^G-nitro-L-arginine methyl ester. $^*P < 0.05$ compared with the respective control group

	Control		L-NAME		Glibenclamide	
	No. individuals studied	pEC_{50}	No. individuals studied	pEC_{50}	No. individuals studied	pEC_{50}
Amrinone	6	3.28 (0.10)	5	3.35 (0.09)	6	3.25 (0.17)
Milrinone	7	3.49 (0.17)	5	2.77 (0.24)*	6	3.46 (0.15)
Enoximone	6	3.29 (0.08)	5	3.41 (0.10)	6	3.49 (0.06)
Theophylline	5	2.72 (0.07)	5	2.69 (0.06)	8	2.76 (0.19)
Dipyridamole	5	4.67 (0.22)	5	4.76 (0.09)	5	4.53 (0.02)

in all experiments. The contractile response to U46619 was not influenced by the administration of L-NAME or glibenclamide. The basal values of the U46619-induced response were comparable in all preparations (table 2). Of the 85 experiments described in table 2, 31 experiments were performed in duplicate, accounting for the total of 116 experiments. Both the contractile response to U46619 and the vasodilator effects of amrinone, milrinone, enoximone, theophylline and dipyridamole were completely reversible on washout.

The contractile responses to the fourth potassium administration and to phenylephrine are shown in table 3. Amrinone was administered in cumulative concentrations of 10^{-8} to 10^{-3} mol $litre^{-1}$. At the highest concentration, amrinone caused relaxation of U46619-induced contraction by 72.4% of the initial value. Milrinone and enoximone were also administered in a concentration range of 10^{-8}–10^{-3} mol $litre^{-1}$. The maximal relaxant effects were 71.4% and 82.2%, respectively. Theophylline proved less potent and effective, as higher doses were required (3.10^{-3} mol $litre^{-1}$) and a lower degree of maximal relaxation (57.8%) was achieved. Dipyridamole

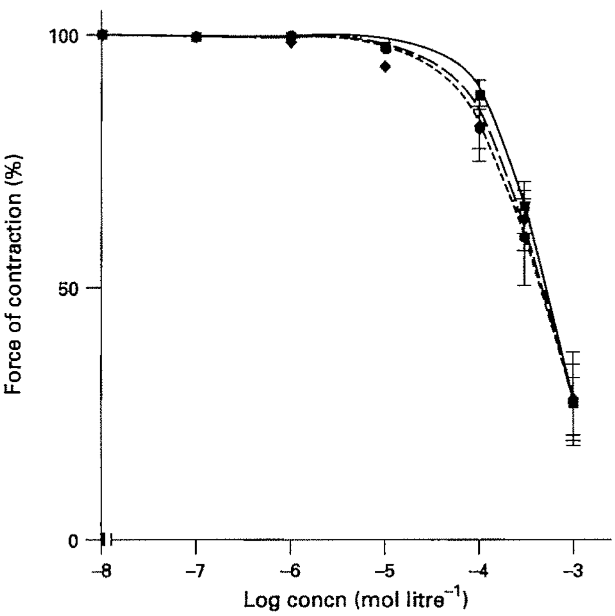


Figure 3 Log concentration-response curve for amrinone in the absence (control (n = 6) (■)) or presence of L-NAME (n = 5) (◆) or glibenclamide (n = 6) ●).

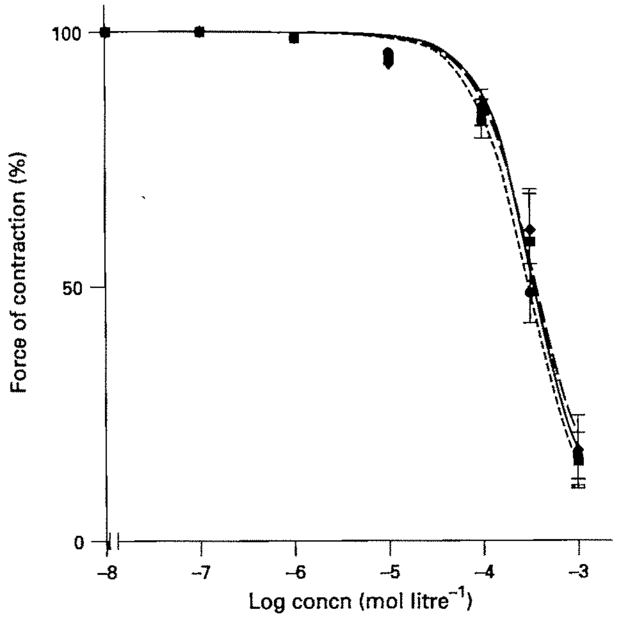


Figure 4 Log concentration-response curve for enoximone in the absence (control ($n = 6$) (■)) or presence of L-NAME ($n = 5$) (◆) or glibenclamide ($n = 6$) (●).

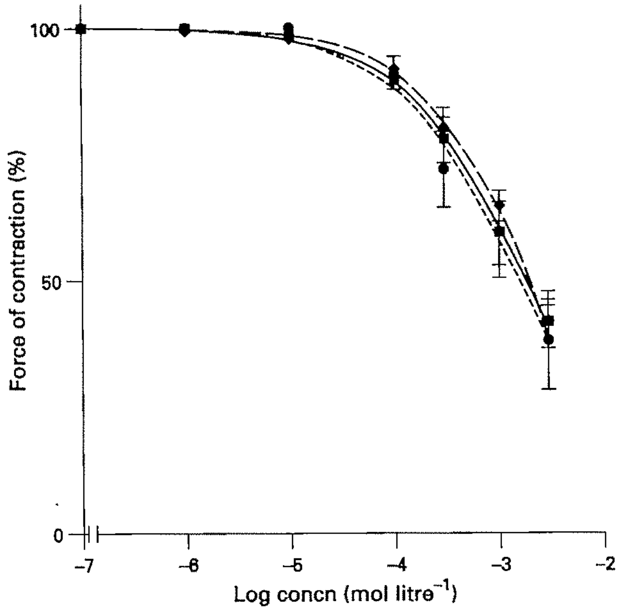


Figure 5 Log concentration-response curve for theophylline in the absence (control ($n = 5$) (■)) or presence of L-NAME ($n = 5$) (◆) or glibenclamide ($n = 8$) (●).

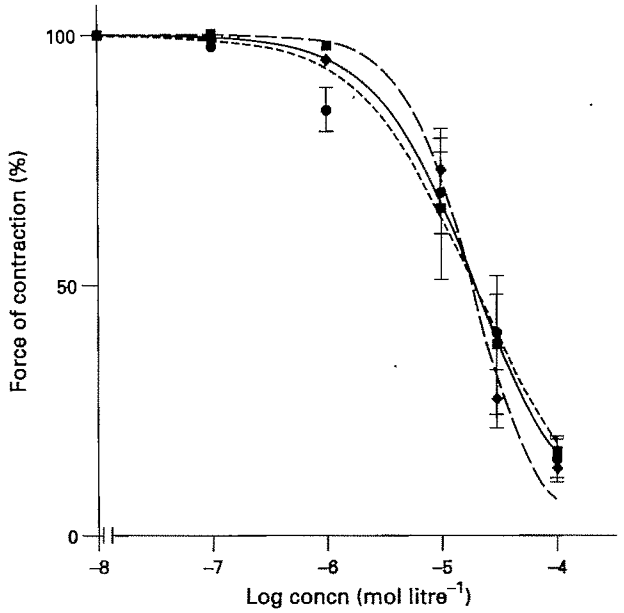


Figure 6 Log concentration-response curve for dipyridamole in the absence (control ($n = 5$) (■)) or presence of L-NAME ($n = 5$) (◆) or glibenclamide ($n = 5$) (●).

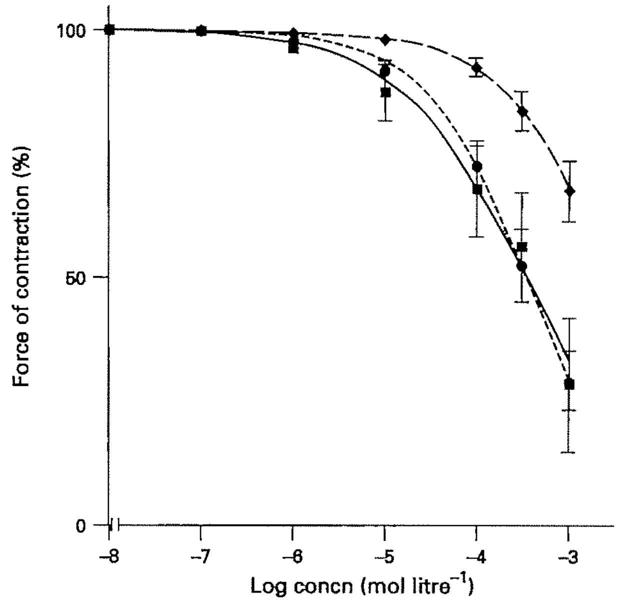


Figure 7 Log concentration-response curve for milrinone in the absence (control ($n = 7$) (■)) or presence of L-NAME ($n = 5$) (◆) or glibenclamide ($n = 6$) (●). In the presence of L-NAME, a significant ($P < 0.05$) rightward shift of the relaxation curve was observed.

concentrations ranged from 10^{-8} to 10^{-4} mol litre^{-1}, resulting in 83% maximum relaxation of the basal value.

Neither L-NAME nor glibenclamide influenced the basal value of the contractile response to U46619 when administered simultaneously with the PDE inhibitors. In addition, neither L-NAME nor glibenclamide influenced the relaxant responses to amrinone, enoximone, theophylline or dipyridamole (table 4 and figs 3–6). However, in the presence of L-NAME a significant ($P < 0.05$) rightward shift was observed in the relaxation curve of milrinone. Accordingly, the pEC$_{50}$ values of milrinone were also influenced by L-NAME: 2.77 (0.24) mol litre^{-1} with L-NAME compared with 3.49 (0.17) mol litre^{-1} without L-NAME ($P < 0.05$) (fig. 7).

Discussion

Using animal models, several investigators have demonstrated that the PDE III inhibitors amrinone, milrinone and enoximone induce vasodilatation as a result of inhibition of cGMP-inhibited (cGI) PDE, thus leading to increased intracellular levels of cAMP [11–14]. The effects of theophylline and dipyridamole on vascular smooth muscle are more complex. The mode of action of theophylline involves both non-specific phosphodiesterase inhibition and adenosine receptor antagonism [24]. In addition, unknown cellular mechanisms appear to play an additional role [25]. Dipyridamole is not only a PDE inhibitor, but also modulates adenosine metabolism, as it inhibits the cellular uptake of adenosine [26, 27].

In the present study, all agents caused concentration-dependent vasodilatation. The concentrations required were rather high compared with the results reported in the literature. However, these data may not be comparable with our results as various types of tissues were used in these studies and were obtained from different species. The use of human vessel preparations provides an obvious advantage when studying the action of agents with an influence on PDE activity, as the distribution of PDE isoenzymes is known to differ considerably between species [28]. Only Lindgren and colleagues used human vessels in their studies, but these tissues were obtained either post mortem or from patients undergoing laparotomy for various abdominal disorders, and not from healthy patients as in our study [11, 29]. Interestingly, these authors showed the importance of the mode of produced contraction on both the magnitude of the relaxant effect and the potency of PDE inhibitors on human vessels *in vitro*. Contractions of isolated arteries induced by high potassium concentrations (K^+ 127 mmol $litre^{-1}$) were more difficult to relax by PDE III inhibitors compared with lower K^+ concentrations (30 mmol $litre^{-1}$) or noradrenaline-induced contractions. Similarly, Harris and colleagues demonstrated a difference in efficacy of PDE III inhibitors in voltage-dependent (K^+ 80 mmol $litre^{-1}$) as opposed to receptor-mediated (U46619) vasoconstriction [30]. The response to the PDE inhibitors in the present study may, therefore, be related partially to the method by which vasoconstriction was induced. Other important factors which may influence the efficacy of PDE inhibitors are the characteristics of the vascular beds from which the human vessels are taken. Marked variations in vascular responsiveness of isolated human coronary, renal and lung arteries have been demonstrated by Lindgren and Andersson [29]. In potassium (30 mmol $litre^{-1}$) contracted lung arteries, cGI-PDE inhibitors (including milrinone 3×10^{-5} mol $litre^{-1}$) were incapable of producing 50% relaxation. In contrast, the agents investigated were significantly more potent and effective in renal and coronary arteries (pEC_{50} for milrinone: 3.2×10^{-6} and 1.7×10^{-6} mol $litre^{-1}$, respectively). This reduced efficacy in both lung arteries in the aforementioned investigation and mammary arteries in our study may indicate low cGI-PDE activities in these particular tissues.

Although not all vessels were used immediately after dissection, but stored in UW organ preservation fluid, there were no differences between the vessel characteristics, including maximal force development and function of endothelium (response to methacholine), between vessels of several minutes to several days old. Therefore, it is unlikely that this preservation technique was responsible for these findings. Thus far there are no reports in the literature that document the preservation of isolated vessel preparations in UW solution. Successful preservation in UW fluid for 72 h, however, has been demonstrated for entire organs taken from animals [31, 32].

In our study, only the vasodilator effects of milrinone were partially endothelium-dependent. The addition of L-NAME 100 μmol $litre^{-1}$ resulted in a significant ($P < 0.05$) increase in the pEC_{50} value of milrinone compared with controls: 2.77 (0.24) *vs* 3.49 (0.17) mol $litre^{-1}$, respectively. So far we cannot explain why the vasodilator profile of milrinone was distinctly different from that of its structurally related analogue, amrinone. Harris and colleagues also described differential relaxant effects of milrinone and amrinone in canine arteries [30]. In their study milrinone proved a more potent vasodilator against receptor-mediated (U46619) as opposed to K^+-induced depolarizations, whereas amrinone appeared equipotent in these conditions. The reason for these different effects could not be elucidated.

Limited data are available in the literature on the interaction between the currently used PDE inhibitors and endothelium. Amrinone was reported to cause vasodilatation by both endothelium-dependent and -independent mechanisms in small pulmonary arteries of rabbits [16]. The vasodilator effects of enoximone in isolated porcine pulmonary arteries were endothelium-independent and unchanged by the addition of L-NAME 10^{-4} mol $litre^{-1}$ [33]. Finally, Kauffman and colleagues demonstrated that the vasodilator effects of milrinone in concentrations ranging from 10^{-7} to 10^{-5} mol $litre^{-1}$ occurred predominantly independent of the presence of an intact endothelium in aortic strips from rats [14]. In addition, these authors demonstrated that a high concentration of milrinone (10^{-4} mol $litre^{-1}$) resulted in increased concentrations of the second messenger cGMP next to enhanced levels of the intracellular mediator cAMP. Furthermore, in the presence of methylene blue, the dose–response curve for milrinone was shifted to the right. Methylene blue acts as an inhibitor of soluble guanyl cyclase and also nitric oxide synthase [34]. Clearly the mechanism by which PDE inhibitors induce vasodilatation is complex, as recent evidence has been obtained demonstrating that cross-interactions between cAMP and cGMP occur at different levels [35, 36].

At high concentrations milrinone acts on PDE IV and PDE V, next to PDE III inhibition [36], PDE IV hydrolyses cAMP, whereas PDE V acts as a specific cGMP hydrolyser. It has been demonstrated that vasodilatation induced by selective PDE IV inhibitors were abolished by both L-NAME and methylene blue, indicating that the effect of PDE IV inhibitors is dependent on nitric oxide production and subsequent activation of soluble guanylate cyclase [36]. Thus, the aforementioned results combined with our data may indicate that milrinone acts as a PDE III inhibitor, independent of endothelial function, at low concentrations, whereas at higher concentrations ($> 10^{-5}$ mol $litre^{-1}$) the inhibitory activity of milrinone on PDE IV, which can be partially abolished by L-NAME becomes more prominent.

The interaction of glibenclamide with milrinone was reported by Fujimoto [37]. In his experiments, inhibition of milrinone-induced vasodilatation by glibenclamide in vascular preparations of rats and guineapigs, was demonstrable only at glibenclamide concentrations as high as 10–30 μmol litre^{-1} [37]. However, at these high concentrations glibenclamide may not act as a specific K_{ATP} channel blocker [38]. In the present investigation glibenclamide 1 μmol litre^{-1} did not influence the vasodilator effect of any of the PDE inhibitors studied, indicating that K_{ATP} channels are not involved in the process of vasodilatation caused by these agents.

In conclusion, L-NAME sensitive nitric oxide release may contribute to the vasodilator properties of milrinone, but not to those of any of the other PDE inhibitors studied. Vasodilatation caused by PDE inhibitors does not appear to involve K_{ATP} channels.

Acknowledgements

We acknowledge the support offered by Dr E. J. F. Timmenga and Dr C. M. A. M. van der Horst, plastic and reconstructive surgeons, in the harvesting of human vascular tissue.

References

1. Butcher RW, Sutherland EW. Adenosine 3′,5′-phosphate in biological materials. *Journal of Biological Chemistry* 1962: 237; 1244–1250.
2. Beavo JA. Multiple isoenzymes of cyclic nucleotide phosphodiesterase. *Advances in Second Messenger and Phosphoprotein Research* 1988; **22**: 1–37.
3. Weishaar RE, Burrows SD, Kobylarz DC, Quade MM, Evans DB. Multiple molecular forms of cyclic nucleotide phosphodiesterase in cardiac and smooth muscle and in platelets. Isolation, characterization and effects of various reference phosphodiesterase inhibitors and cardiotonic agents. *Biochemical Pharmacology 1986*; **5**: 787–800.
4. Thompson WJ. Cyclic nucleotide phosphodiesterases: Pharmacology, biochemistry and function. *Pharmacology and Therapeutics* 1991; **51**: 13–33.
5. Nicholson CD, Challis RAJ, Shahid M. Differential modulation of tissue function and therapeutic potential of selective inhibitors of cyclic nucleotide phosphodiesterase isoenzymes. *Trends in Pharmacological Sciences* **1991**; **12**: 19–27.
6. Packer M, Carver JR, Rodeheffer RJ, Ivanoe RJ, DiBianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, Kukin ML, Mallis GI, Sollano JA, Shannon J, Tandon PK, De Mets DL. Effect of oral milrinone on mortality in severe chronic heart failure: Promise study. *New England Journal of Medicine* 1991; **325**: 1468–1475.
7. DiBianco R, Shabetia R, Kostuk W, Moran J, Schlant RC, Wright R. A comparison of oral milrinone, digoxin and their combination in the treatment of chronic heart failure. *New England Journal of Medicine* 1989; **320**: 677–683.
8. Uretsky BF, Jessup M, Konstam MA, Dec W, Leier CV, Benotti J, Murali S, Herrmann HC, Sandberg JA. For the enoximone multicenter trial group. Multicenter trial of oral enoximone in patients with moderate to moderately severe congestive heart failure. *Circulation* 1990; **82**: 774–780.
9. Dupuis JY, Bondy R, Cattran C, Nathan HJ, Wynands JE. Amrinone and dobutamine as primary treatment of low cardiac output syndrome following coronary artery surgery: A comparison of their effects on hemodynamics and outcome. *Journal of Cardiothoracic and Vascular Anesthesia* 1992; **6**: 542–553.
10. Caldicott LD, Hawley K, Heppel R, Woodmansey PA, Channer KS. Intravenous enoximone or dobutamine for severe heart failure after acute myocardial infarction: a randomized double blind trial. *European Heart Journal* 1993; **14**: 696–700.
11. Lindgren S, Andersson KE, Belfrage P, Degerman E, Manganiello VC. Relaxant effects of the selective phosphodiesterase inhibitors milrinone and OPC 3911 on isolated human mesenteric vessels. *Pharmacology and Toxicology* 1989; **64**: 440–445.
12. Silver PJ, Lepore RE, O'Connor B, Lemp BM, Hamel LT, Bentley RG, Harris, AL. Inhibition of the low K_m cyclic AMP system in vascular smooth muscle by milrinone. *Journal of Pharmacology and Experimental Therapeutics* 1988; **247**: 34–42.
13. Itoh H, Kusagawa M, Shimomura A, Suga T, Ito M, Konishi T, Nakano T. Ca^{2+} dependent and Ca^{2+} independent vasorelaxation induced by cardiotonic phosphodiesterase inhibitors. *European Journal of Pharmacology* 1993; **240**: 57–66.
14. Kauffman RF, Schenck KW, Utterbach BG, Crowe G, Cohen ML. In vitro vascular relaxation by new inotropic agents: Relationship to phosphodiesterase inhibition and cardiac nucleotides. *Journal of Pharmacology and Experimental Therapeutics* 1987; **242**: 864–872.
15. Weishaar RE, Burrows SD, Kobylarz DC, Quade MD, Evans DB. Multiple molecular forms of cyclic nucleotide phosphodiesterase in cardiac and smooth muscle and in platelets: Isolation, characterization and effects of various reference phosphodiesterase inhibitors and cardiotonic agents. *Biochemical Pharmacology* 1986; **35**: 787–800.
16. Clarke WR, Soltow LOG. Amrinone causes vasodilation by both endothelium-independent and endothelium dependent mechanisms in small pulmonary arteries. *American Review of Respiratory Diseases* 1991; (Suppl A773).
17. Rosenblum WI, Shimizu T, Nelson GH. Interaction of endothelium with dilation produced by inhibitors of cyclic nuclide diesterases in mouse brain arterioles in vivo. *Stroke* 1993; **24**: 266–270.
18. Martin W, Furchgott RF, Villani GM, Jothianandan D. Phosphodiesterase inhibitors induce endothelium-dependent relaxation of rat and rabbit aorta by potentiating the effects of spontaneously released endothelium-derived relaxing factor. *Journal of Pharmacology and Experimental Therapeutics* 1986; **237**: 539–547.
19. Grover GJ, Sleph PG, Dzwonczyk S. Role of myocardial ATP-sensitive potassium channels in mediating preconditioning in the dog heart and their possible interaction with adenosine A_1 receptors. *Circulation* 1992; **86**: 1310–1316.
20. Gross GJ, Auchampach JA. Blockade of ATP-sensitive potassium channels prevents myocardial preconditioning in dogs. *Circulation Research* 1992; **70**: 223–233.
21. Southard JH, Van Gulik TM, Ametani MS, Vreugdenhil PK, Lindell SL, Pinaar BL, Belzer FO. Important components of the UW solution. *Transplantation* 1990; **49**, 251–257.
22. Mulvany MJ, Halpern W. Mechanical properties of vascular smooth muscle cells in situ. *Nature* (*London*) 1976; **260**: 617–618.
23. Mulvany MJ, Halpern W. Contractile properties of small arterial resistance vessels in spontaneously hypertensive and normotensive rats. *Circulation Research* 1977; **41**: 10–26.
24. Fredholm BB, Persson CGA. Xanthine derivatives as adenosine receptor antagonists. *European Journal of Pharmacology* 1982; **81**: 673–676.
25. Persson CGA, Andersson KE, Kjellin G. Effects of enprofylline and theophylline may show the role of adenosine. *Life Sciences* 1986; **38**: 1057–1072.
26. Kubler W, Spieckermann PA, Bretschneider HJ. Influence of dipyridamole (Persantin) on myocardial adenosine metabolism. *Journal of Molecular and Cellular Cardiology* 1970; **1**: 23–27.
27. Klabunde RE. Effects of dipyridamol on postischemic vasodilation and extracellular adenosine. *American Journal of Physiology* 1983; **244**: H273–H280.
28. Weishaar RE, Kobylarz-Singer DC, Steffen RP, Kaplan HR. Subclasses of cyclic AMP, specific phosphodiesterase in left ventricular muscle and their involvement in myocardial contractility. *Circulation Research* 1987; **61**: 539–547.
29. Lindgren S, Andersson KE. Effects of selective phosphodiesterase inhibitors on isolated coronary, lung and renal arteries from man and rat. *Acta Physiologica Scandinavica* 1991; **142**: 77–82.

30. Harris AL, Grant AM, Silver PJ, Evans DB, Alousi AA. Differential vasorelaxant effects of milrinone and amrinone on contractile responses of canine coronary, cerebral, and renal arteries. *Journal of Cardiovascular Pharmacology* 1989; **13**: 238–244.
31. Ploeg RJ, Goossens D, McAnulty JF, Stouthard JH, Belzer FO. Successful 72 hour cold storage of dog kidneys with UW solution. *Transplantation* 1988; **46**: 191–196.
32. Wahlberg JA, Love R, Landegaard L, Stouthard JH, Belzer FO. 72 hours preservation of the canine pancreas. *Transplantation* 1987; **43**: 5–8.
33. Butt AY, Dinh-Xuan AT, Pepke-Zaba J, Cremona G, Clelland CA, Higenbottam TW. In vitro pulmonary vasorelaxant effect of the phosphodiesterase inhibitor enoximone. *Angiology* 1993; **12**: 289–294.
34. Mayer B, Brunner F, Schmidt K. Novel actions of methylene blue. *European Heart Journal* 1993; **14**: (Suppl. I) 22–26.
35. Jiang J, Colbran JL, Francis SH, Corbin JD. Direct evidence for cross-activation of cGMP-dependent protein kinase by cAMP in pig coronary arteries. *Journal of Biochemical Chemistry* 1992; **267**: 1015–1019.
36. Lugnier C, Komas N. Modulation of vascular cyclic nucleotide phosphodiesterases by cyclic GMP: role in vasodilatation. *European Heart Journal* 1993; **14** (Suppl. I): 141–148.
37. Fujimoto S. Effects of pimobendan, its active metabolite UD-CG 212 and milrinone on isolated blood vessels. *European Journal of Pharmacology* 1994; **265**: 159–166.
38. Ashcroft FM. Adenosine 5′-triphosphate-sensitive potassium channels. *Annual Review of Neuroscience* 1988; **11**: 97.

British Journal of Anaesthesia 1996; **76**: 130–132

Effect of pneumoperitoneum and Trendelenburg position on gastro–oesophageal reflux and lower oesophageal sphincter pressure

J. P. TOURNADRE, D. CHASSARD, K. R. BERRADA AND P. BOULETREAU

Summary

We have measured the effect of pneumoperitoneum and the Trendelenburg position on lower oesophageal sphincter (LOSP) and barrier pressures (BrP) in 11 anaesthetized pigs while measuring the incidence of gastro–oesophageal reflux with a pH electrode. Propofol in combination with sufentanil had no effect on LOSP or BrP. Adoption of the Trendelenburg position with a pneumoperitoneum of 15 mm Hg resulted in a significant increase in LOSP ($P < 0.002$) and BrP ($P < 0.001$). However, in two of 11 pigs who had the lowest LOSP before induction, there was regurgitation. (*Br. J. Anaesth.* 1996; **76**: 130–132)

Key words

Complications, regurgitation. Gastrointestinal tract, lower oesophageal sphincter. Position, Trendelenburg. Surgery, laparoscopy. Pig.

Factors which increase lower oesophageal sphincter pressure (LOSP) usually also increase oesophageal barrier pressure (BrP = LOSP − gastric pressure). To date, only one study found that increased intra-abdominal pressure and Trendelenburg position resulted in an increase in LOSP and it was concluded that laparoscopy did not necessarily increase the likelihood of regurgitation [1]. However, reflux was not measured and oesophageal pressures were not recorded before induction of anaesthesia. We have therefore studied in pigs the effects of anaesthesia, pneumoperitoneum and Trendelenburg position on LOSP and gastro-oesophageal reflux.

Materials and methods

After obtaining approval from our Institutional Animal Care Committee, we studied 11 pigs (weight 22–25 kg). Ketamine 8 mg kg^{-1} i.m. was given as premedication after a 12-h fast. Anaesthesia was induced with propofol 5 mg kg^{-1}, sufentanil 3 μg kg^{-1} and pancuronium 0.1 mg kg^{-1} i.v. The trachea was intubated with a 6-mm cuffed tube and the lungs ventilated artificially using a MMS 107 ventilator (MMS, Pau, France) with a tidal volume of 15 ml kg^{-1} at a ventilatory frequency of 12–15 b.p.m. (normocapnia at baseline using an Engström Eliza capnograph). Anaesthesia was maintained with a continuous infusion of propofol 10 mg kg^{-1} h^{-1}. Carbon dioxide was insufflated through a Veress needle inserted through a 2-cm abdominal midline incision. Intra-abdominal pressure was maintained at 15 mm Hg (Wolf, Knittlingen, Germany).

The technique of oesophageal manometry has been described previously [2, 3]. Briefly, LOSP, gastric (GP) and intraperitoneal pressures (IPP) were measured with the pig in the supine position using perfused polyethylene catheters connected to pressure transducers (Bentley Trantec, Irvine, CA, USA). Recordings of LOSP were made at end-expiration by a "pull-through" manoeuvre. Transducers were zeroed at the level of the midchest position. Before each investigation, the system was calibrated in a water column (0–50 cm H_2O) and perfused continuously using a low compliance system (SC 2000 pump, Sky Electronics). Pressures were recorded using a multiple channel recording system (Kontron Medical) before induction (T0), after induction (T1), at an intra-abdominal pressure of 15 mm Hg (T3), at a pressure of 15 mm Hg with 15° of Trendelenburg position (T4) and finally with the pig supine again (T5).

Oesophageal pH was measured continuously using a bipolar glass electrode (Ecosecur pH recorder, Tacussel). The electrode was calibrated before each set of measurements with standardized solutions of buffer at pH 3 and 7. The electrode was advanced until gastric pH was recorded. It was then withdrawn to the gastro–oesophageal junction, recognized by an abrupt increase in pH, and finally positioned 5 cm above the junction. Reflux was defined as an abrupt decrease in oesophageal pH to less than 4 [2, 4].

Statistical significance was determined using a paired Wilcoxon test. $P < 0.05$ was considered statistically significant.

Results

Baseline LOSP and BrP were in the normal range for pigs. LOSP was not affected by anaesthesia and BrP remained above 10 mm Hg (table 1).

The Trendelenburg position, pneumoperitoneum, or both, increased LOSP, while significant increases in BrP and LOSP were noted only after

---

J. P. TOURNADRE, MD, D. CHASSARD, MD, K. R. BERRADA, MD, P. BOULETREAU, MD, Service d'Anesthésie-Réanimation, Hôpital de l'Hôtel-Dieu, 69002 Lyon, France. Accepted for publication: August 7, 1995.

Correspondence to D. C.

Table 1 Effect of anaesthesia, pneumoperitoneum and Trendelenburg position on lower oesophageal sphincter pressure (LOSP) and barrier pressure (BrP = LOSP − gastric pressure) in anaesthetized pigs (mean (SD)). IPP = Intraperitoneal pressure. $^{**}P < 0.01$, $^{***}P < 0.001$

	Baseline	After induction	IPP of 15 mm Hg	Trendelenburg + IPP of 15 mm Hg	IPP of 15 mm Hg
LOSP (mm Hg)	19.1 (9.3)	16.4 (7.8)	31.0 (14.5)**	42.6 (19.7)**	31.0 (14.8)**
BrP (mm Hg)	15.2 (8.8)	12.5 (8.5)	13.7 (12.8)	20.9 (17.8)***	13.7 (12.4)

the combination of pneumoperitoneum and Trendelenburg position. During the Trendelenburg position, the increase in LOSP was greater than the change in IPP (LOSP: 42.6 − 16.4 = 26.2 mm Hg *vs* IPP = 15 mm Hg) (table 1). Two of 11 pigs exhibited prolonged gastro–oesophageal reflux during pneumoperitoneum: both had a BrP lower than 0 mm Hg (0 and −2 mm Hg) at the time of reflux. Before and after induction, BrP was lower in these two pigs with reflux than in pigs without reflux: 7 (SD 1) compared with 17.1 (8.7) mm Hg and 5 (1) compared with 14.2 (6.5) mm Hg, respectively.

When the Trendelenburg position was reversed and the pigs placed supine, gastric pressure decreased to values similar to those recorded during pneumoperitoneum.

Discussion

We have demonstrated that lower oesophageal sphincter pressure increases significantly in response to increases in intra-abdominal pressure. However, in some animals, there was gastro–oesophageal reflux.

As in humans, the musculature of the porcine distal oesophagus consists of smooth muscle fibres [5]. Recent studies have shown that the pressure at the LOS is created not only by contraction of these smooth muscles but also by the striated muscle of the crural diaphragm [6]. Previous studies have demonstrated that drugs commonly used during anaesthesia such as atropine [7], benzodiazepines [2], morphine [2], thiopentone [3] and halothane [8] can affect the competency of the lower oesophageal sphincter. In contrast, ketamine has no effect on LOSP [9]. In a clinical study, Roberts and Goodman [10] did not observe any reflux episodes in 63 patients anaesthetized with propofol and fentanyl. In our study, we demonstrated that propofol associated with sufentanil had no effect on LOSP and BrP in pigs.

After adopting the Trendelenburg position, as the increase in LOS pressure was far greater than the change in gastric pressure, BrP increased. Heijke, Smith and Key [11] showed that adoption of the Trendelenburg position alone (15° and 30°) did not change BrP in female patients during balanced anaesthesia, and Lind, Warrian and Wankling [7] found that increasing IPP resulted in an increase in BrP. Jones, Mitchell and Hindocha [1] reported that the combination of Trendelenburg 15° and IPP at 20 mm Hg resulted in an increase in BrP, results similar to our findings. Increasing intra-abdominal or intragastric pressures by straight-leg raising or abdominal compression results in a concomitant increase in LOS pressure in animals as in human volunteers [12]. During anaesthesia, this adaptive response to increases in gastric pressure has been reported to be mediated partially via a cholinergic pathway as atropine reduced LOS tone [6].

During laparoscopy, carbon dioxide insufflation increases IPP and gastric pressure. Some clinical studies have evaluated the incidence of regurgitation during laparoscopy as 2–20% [10, 13], an incidence no greater than that during other surgical procedures [14]. We also found a 20% incidence of reflux (two of 11 pigs). Jones, Mitchell and Hindocha [1] have shown the presence of an adaptive response in LOSP in response to peritoneal insufflation up to 30 cm H_2O. Heijke, Smith and Key [11] reported a small increase in gastric pressure during 30° Trendelenburg position, but BrP was not affected. It was concluded from these manometric studies that laparoscopy does not increase the risk of regurgitation. However, these manometric studies are not conclusive as intraoperative recording of oesophageal pH was not undertaken. In contrast, our results showed that reflux may occur in some animals because the adaptive response was not always present. We noted in two pigs that BrP was lower than 0 mm Hg during episodes of reflux and that these pigs had the lowest LOSP and BrP values throughout the study. Although it is well established that there is a relationship between a decrease in LOSP and reflux [15], it is not possible at this time to define BrP or LOSP values below which reflux will occur. Any decrease in BrP during anaesthesia would be expected to increase the risk of regurgitation and this is particularly true in situations where LOSP is initially low.

From this study we suggest that in an individual patient it is not possible to predict that the adaptive response of the LOS protects against regurgitation during laparoscopy.

References

1. Jones MJ, Mitchell RW, Hindocha N. Effect of increased intra-abdominal pressure during laparoscopy on the lower esophageal sphincter. *Anesthesia and Analgesia* 1989; **68**: 63–65.
2. Hall AW, Moossa AR, Clark J, Cooley GR, Skinner DB. The effect of premedication drugs on the lower oesophageal high pressure zone and reflux status of Rhesus monkeys and man. *Gut* 1975; **16**: 347–352.
3. Smith G, Dalling R, Williams TIR. Gastro–oesophageal pressure gradient changes produced by induction of anaesthesia and suxamethonium. *British Journal of Anaesthesia* 1978; **50**: 1137–1142.

4. Inauen W, Emde C, Armstrong D, Bettschen HU, Huber T, Scheurer U, Blum AL, Halter F, Merki HS. Effect of ranitidine and cisapride on acid reflux and oesophageal motility in patients with reflux oesophagitis: a 24-hour ambulatory combined pH and manometry study. *Gut* 1993; **34**: 1025–1031.
5. Weisbrodt NW. Neuromuscular organisation of esophageal and pharyngeal motility. *Archives of Internal Medicine* 1976; **136**: 524–531.
6. Mittal RK, Fisher M, McCallum RW, Rochester DF, Dent J, Sluss J. Human lower esophageal sphincter pressure response to increased intra-abdominal pressure. *American Journal of Physiology* 1990; **258**: G624–G630.
7. Lind JF, Warrian WG, Wankling WJ. Responses of the gastroesophageal junctional zone to increases in abdominal pressure. *Canadian Journal of Surgery* 1966; **9**: 32–38.
8. Senhati GH, Frey R, Star EG. The action of inhalation anaesthetics upon the lower oesophageal sphincter. *Acta Anaesthesiologica Belgica* 1980; **31**: 91–98.
9. Chen K, Pan J, Ji X. The effects of three kinds of anaesthesia on lower oesophageal sphincter pressure. *Canadian Journal of Anaesthesia* 1990; **37**: S59.
10. Roberts CJ, Goodman NW. Gastro-oesophageal reflux during elective laparoscopy. *Anaesthesia* 1990; **45**: 1009–1011.
11. Heijke SA, Smith G, Key A. The effect of the Trendelenburg position on lower oesophageal sphincter tone. *Anaesthesia* 1991; **46**: 185–187.
12. Landers BR, Jamieson GG. Response of porcine lower esophageal sphincter to increasing intraabdominal pressure. *Digestive Diseases and Sciences* 1987; **32**: 272–279.
13. Duffy BL. Regurgitation during pelvic laparoscopy. *British Journal of Anaesthesia* 1979; **51**: 1089–1090.
14. Kallos T, Lampe KF, Orkin FK. Pulmonary aspiration of gastric contents. In: *Complications in Anesthesiology*. Philadelphia: JB Lippincott, 1993; 152–153.
15. Haddad JK. Relation of gastroesophageal reflux to yield sphincter pressures. *Gastroenterology* 1970; **58**: 175.

British Journal of Anaesthesia 1996; **76**: 133–148

REVIEW ARTICLE

Recent developments in the pathophysiology and management of pre-eclampsia

M. C. MUSHAMBI, A. W. HALLIGAN AND K. WILLIAMSON

Fits occurring in pregnant women were recognized and recorded as early as the 4th century BC by Hippocrates [94]. The condition was termed eclampsia—a Greek word which translates literally as 'shine forth'—implying a sudden development. Little was known about eclampsia until 1843, when Lever of Guy's Hospital found that many of the women who had fits also had albumin in their urine [74]. However, it was not until the widespread use of the sphygmomanometer that the condition was known to be associated with raised systemic arterial pressure. Because it was recognized that albuminuria and hypertension could precede the onset of fits, the term pre-eclampsia was coined although this nomenclature is now criticized because only a small proportion of patients with pre-eclampsia subsequently develop eclampsia.

Pre-eclampsia is a multisystem disorder of unknown aetiology and unique to pregnant women after 20 weeks' gestation. In the UK, 18.6 % of maternal deaths are caused by hypertensive diseases [42]. Hypertensive disorders of pregnancy are common, affecting 10.6 % of pregnant women [109]. Pre-eclampsia (i.e. proteinuric hypertension) affects 5.8 % of primigravidas, and 0.4 % of secundagravid women [84]. While premature labour is the leading cause of very low birthweight neonates, the next most common cause is hypertension which accounts for 23 % of all viable very low birthweight singleton infants [2].

Pre-eclampsia is a progressive disease with a very variable mode of presentation and rate of progression. Of all the features of the syndrome, hypertension, pregnancy-induced proteinuria, excessive weight gain and oedema are the classic clinical manifestations. Other features include, thrombocytopenia, hyperuricaemia, abnormal liver function tests, haemoconcentration, hypoalbuminaemia and eclampsia.

Eclampsia is a rare but serious complication of pre-eclampsia; it complicates about 1:2000 deliveries in Europe and the developed countries [45] and from 1:100 to 1:1700 deliveries in developing countries [34]. The higher incidence in countries with poor economies is thought to result from inadequate antenatal care with late presentation of patients to hospital. In the UK, 38 % of convulsions occur before the diagnosis of proteinuric pre-eclampsia is made and 44 % occur in the postpartum period. Teenage patients and mothers with multiple pregnancies have a higher risk of developing fits. Eclampsia which occurs antenatally carries more complications than when the condition develops in the intrapartum or postpartum periods [45]. In the UK, eclampsia contributes to 10 % of maternal deaths [42]. The complications of eclampsia are shown in table 1.

Despite decades of research, the pathogenesis of pre-eclampsia is still not understood fully but it is generally accepted that the underlying pathological changes occur in the placenta and placental bed. Early recognition of the syndrome still presents a challenge to clinicians as there is no specific diagnostic test, and treatment is based on management of symptoms and prevention of complications rather than specific therapy.

Classification

The classification and definition of hypertensive disorders during pregnancy continue to generate controversy. The current recommended classification is that by the International Society for the Study of Hypertension (ISSHP) [38]. This recognizes four categories in pregnancy (table 2). Gestational or pregnancy-induced hypertension is caused by the pregnancy itself whereas chronic hypertension refers to pre-existing elevation in arterial pressure.

Definition and diagnosis

Pre-eclampsia cannot be defined accurately until its cause is known. For many years, the syndrome was considered to comprise hypertension, oedema and proteinuria occurring after 20 weeks' gestation, not because these were the most important features but because, historically they were the first to be

(*Br. J. Anaesth.* 1996; **76**: 133–148)

Key words

Arterial pressure, hypertension. HELLP syndrome. Complications, pre-eclampsia.

M. C. MUSHAMBI, FRCA (Department of Anaesthesia); A. W. HALLIGAN, MD, MRCOG, K. WILLIAMSON, FRCS, MRCOG (Department of Obstetrics and Gynaecology); Leicester Royal Infirmary, Leicester LE1 5WW.

Correspondence to M. C. M.

Table 1 Complications of eclampsia [119]

		Percentage incidence
1.	HELLP syndrome	9.8
2.	Abruptio placentae	9.8
3.	Disseminated intravascular coagulation (DIC)	5.1
4.	Acute renal failure	4.7
5.	Pulmonary oedema	4.3
6.	Cardiorespiratory arrest	3.1
7.	Aspiration of gastric contents	2.0
8.	Maternal death	0.4
9.	Perinatal mortality	11.8
10.	Neurological abnormalities	
	Transient deficit	3.2
	Transient cortical blindness	2.4
	Retinal detachment	0.8
	Postpartum psychosis	0.8
	Comatose state	1.2
	Cerebral death	0.4
	Intracerebral bleed	0

Table 2 Classification of hypertensive diseases in pregnancy [38]

A. Gestational hypertension and/or proteinuria developing during pregnancy after 20 weeks' gestation in a previously normotensive, non-proteinuric woman.
  1. Hypertension without proteinuria
  2. Proteinuria without hypertension
  3. Gestational proteinuric hypertension (pre-eclampsia).

B. Chronic hypertension and chronic renal disease
  1. Chronic hypertension without proteinuria
  2. Chronic renal disease diagnosed before, during or persisting after pregnancy
  3. Chronic hypertension with superimposed pre-eclampsia.

C. Unclassified hypertension and/or proteinuria which is found at the first antenatal visit after 20 weeks' gestation in a woman whose past hypertensive status is unknown.

D. Eclampsia is the occurrence of generalized convulsions during pregnancy, labour or within 7 days of delivery in the absence of epilepsy or another condition predisposing to convulsions.

Table 3 Definition of pre-eclampsia [38]

1.	Gestation	> 20 weeks
2.	Arterial pressure	Diastolic > 110 mm Hg on any one occasion OR Diastolic > 90 mm Hg on 2 or more occasions at least 4 h apart
3.	Proteinuria	> 300 mg in 24 h OR 2 clean-catch mid-stream or catheter specimens of urine collected at least 4 h apart with: (1) 1 g albumin litre^{-1} OR $\geqslant$ 2+ on reagent strip OR (2) 0.3 g albumin litre^{-1} or $\geqslant$ 1+ on reagent strip if urine pH is < 8 or specific gravity is < 1.030
4.	Oedema	Not essential for diagnosis

recognized. Despite the problems of definition, the ISSH has produced a useful pragmatic version which is shown in table 3.

Oedema is not included in this definition because moderate degrees of oedema may be detected in 80% of normotensive pregnant women, most of whom are healthy. Pathological oedema affects 85% of women with proteinuric pre-eclampsia; it appears relatively suddenly and is associated with accelerated weight gain. However, eclampsia without oedema has been recognized for many years as particularly dangerous while more recently, 32% of a series of eclamptic patients were noted to have no oedema [119]. The perinatal mortality in pre-eclampsia without oedema is higher than when the condition exists with oedema.

The difficulties with definition of hypertension in pregnancy are caused partly by problems in measurement of arterial pressure and partly by the controversy in identifying the optimal threshold level for diastolic pressure.

MEASUREMENT OF ARTERIAL PRESSURE

Problems in measuring arterial pressure focus accurately on three areas: (1) use of the correct size of cuff for each patient, (2) correct positioning of the patient during measurement, and (3) use of the correct phase of the Korotkoff sounds in measuring diastolic pressure.

The cuff size

It is generally agreed that hypertension in obese patients is overdiagnosed if the cuff is too small in relation to the arm circumference. When the arm circumference (AC) is less than 33 cm, a regular cuff (12 × 23 cm) should be used, a larger cuff (15 × 33 cm) if the AC is 33–41 cm and a thigh cuff (18 × 36 cm) if the AC is greater than 41 cm [88].

Position of the patient

Indirect arterial pressure should be measured with the cuff at the level of the heart. If it is above or below this level, the pressure in the brachial artery varies because of hydrostatic forces. Thus, standardization of posture and arm position is crucial. In the USA, it is recommended that arterial pressure is measured in the sitting position with the cuff at the level of the heart [92]. In the UK and in accordance with the ISSH [38], it is suggested that arterial pressure is measured with the patient lying on a bed or couch on the right side at 30 degrees of lateral tilt and with the sphygmomanometer cuff and heart at the same level.

Korotkoff sounds

Korotkoff sounds are produced by vibrations in the arterial wall as the pressure cuff is deflated. Phase I of the Korotkoff sounds defines systolic pressure. Diastolic pressure is defined by either phase IV (muffling of sounds) or V (disappearance of sounds). Phase IV is accepted by the ISSH and is generally used by midwives in the UK. Phase V is used in the USA. There is considerable controversy regarding whether K4 or K5 should be used in pregnancy. The reason why K4 has been adopted by many organizations appears to be based primarily on a study suggesting that a significant but undefined proportion of women have sounds audible down to zero cuff pressure [85]. This fact has not been sub-

Table 4 Definition of severe pre-eclampsia [145]

1. Arterial pressure > 160 mm Hg systolic or > 110 mm Hg diastolic on two occasions at least 6 h apart
2. Proteinuria > 5 g in 24 h or > 3+ on dipstick
3. Oliguria < 400 ml in 24 h
4. Cerebral signs—headache, blurred vision or altered consciousness
5. Pulmonary oedema or cyanosis
6. Epigastric or right upper quadrant pain
7. Impaired liver function
8. Hepatic rupture
9. Thrombocytopenia
10. HELLP syndrome

stantiated though it has been endorsed by leading authorities recommending the use of K4 [38].

DEFINITION OF HYPERTENSION

There is still controversy on the threshold level of arterial pressure at which the state of hypertension is said to be present. The ISSH defines hypertension in pregnancy as: (1) one reading of diastolic pressure exceeding 110 mm Hg, or (2) two consecutive diastolic arterial pressures of 90 mm Hg or greater at an interval of at least 4 h [38].

The definition is simple, precise and convenient, and it corresponds with statistical studies (a diastolic arterial pressure of 90 mm Hg correlates with approximately 3 standard deviations (SD) above the mean pressure in early and mid-pregnancy, 2 SD at 34 to 39 weeks and 1.5 SD at term) [37]. Furthermore, a diastolic pressure exceeding 90 mm Hg correlates with perinatal mortality [50]. In other proposed definitions [92, 106] it has been suggested that the degree of increase in diastolic pressure is important. Recently, it has been proposed that a combination of a first diastolic reading of less than 90 mm Hg, a subsequent increase of 25 mm Hg or more and a maximum diastolic pressure of 90 mm Hg or more may identify a group of pregnant women with pre-eclampsia more accurately than either the increase in pressure or absolute level [106]. However, there are limited epidemiological data on the clinical importance of increments in diastolic pressure and the use of two measurements of pressure makes this more complex; furthermore, there is a risk of misdiagnosis if the arterial pressure is abnormally low at any stage during early pregnancy.

Proteinuria is defined as the excretion of 0.3 g protein or more within 24 h or a measurement of 1+ or more using reagent strips or dipstick tests obtained from two samples of either 'clean-catch' or catheter samples of urine at least 4 h apart [38]. Proteinuria not only strengthens the diagnosis but it also indicates a poorer prognosis for both the mother and baby than when it is absent [91].

In the absence of trophoblastic disease, pregnancy-induced hypertension rarely occurs before 20 weeks' gestation. Hypertension and/or proteinuria diagnosed before 20 weeks usually results from pre-existing chronic hypertension or renal disease.

Pre-eclampsia is a progressive syndrome but unfortunately it is a very variable condition, and at any given time it is difficult to stage the condition or prognosticate on its progress.

Pragmatically, when managing patients with pre-eclampsia it is useful to be able to classify pre-eclampsia into mild or severe forms as the latter is associated with increased maternal and fetal morbidity and therefore more aggressive management is indicated. While many authors differ in their definitions it seems to be generally accepted that severe pre-eclampsia exists if one or more of the conditions described in table 4 are present.

Pathophysiology

Pre-eclampsia is a syndrome which affects virtually all maternal organ systems. The underlying pathophysiology is still not fully elucidated but the common pathological feature in the placenta, kidneys and brain is vascular endothelial damage and dysfunction [82], the major pathological changes are in the placental bed.

In normal pregnancy, the endothelium, internal elastic lamina and muscular layer of the media of the spiral arteries supplying the placenta are replaced by trophoblast and amorphous matrix containing fibrin [82]. These changes transform the vascular supply to a low pressure and high flow system which meets the needs of the fetus and placenta. Pre-eclampsia is associated with failure of, or incomplete trophoblastic invasion of, the spiral arteries resulting in narrowed spiral arteries and subsequent placental ischaemia. Subsequently, the abnormal placenta may release one or more factors which damage vascular endothelial cells throughout the mother (fig. 1) leading to multisystem dysfunction [108, 112] (fig. 2).

The endothelial cell has many important functions including maintenance of fluid compartments, prevention of intravascular coagulation, modification of contractile responses in the smooth muscle wall [51] and maintenance of immune and inflammatory responses. When injured, the endothelial cells not only lose these responses but also they produce procoagulants, vasoconstrictors and mitogens. Blood vessels in pre-eclamptic mothers demonstrate increased capillary permeability [51] with exaggerated responses to angiotensin II [39]. The increased pressor sensitivity leads to profound vasospasm and reduced organ perfusion changes which are characteristic of the disorder.

Many investigations have recorded maternal endothelial dysfunction in pre-eclampsia, e.g. maternal vascular prostacyclin production is reduced in patients with pre-eclampsia, probably because of endothelial dysfunction [82]. Other markers of endothelial damage include increased von Willebrand factor [105] and fibronectin levels [136]. Activated neutrophils release substances which can mediate vascular damage. These include contents of the neutrophil granules such as elastase and other proteases. Activation has been shown to occur in pre-eclampsia [53, 82]. In a recent study it has been shown that enhanced free radical formation occurs in patients with pre-eclampsia and this may augment endothelial damage and exacerbate the disease process [40] (see fig. 1).

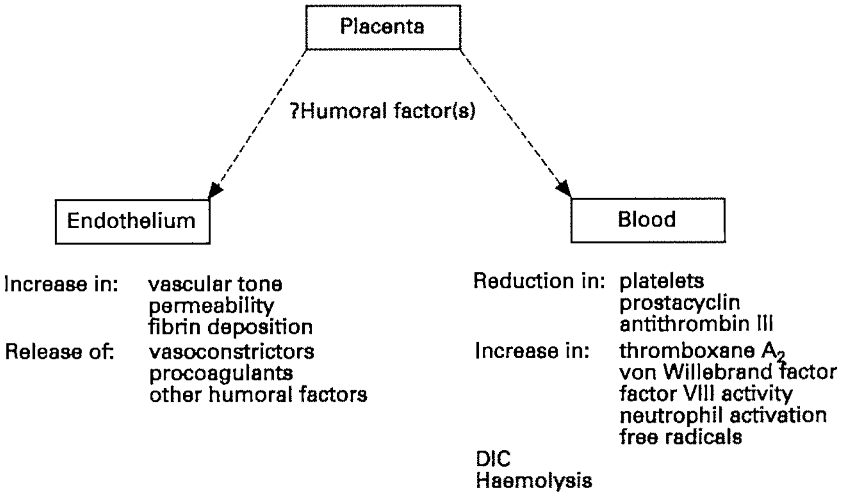


Figure 1 Major initiating changes in the aetiology of pre-eclampsia. The primary trigger may be placental ischaemia. (DIC = disseminated intravascular coagulation.)

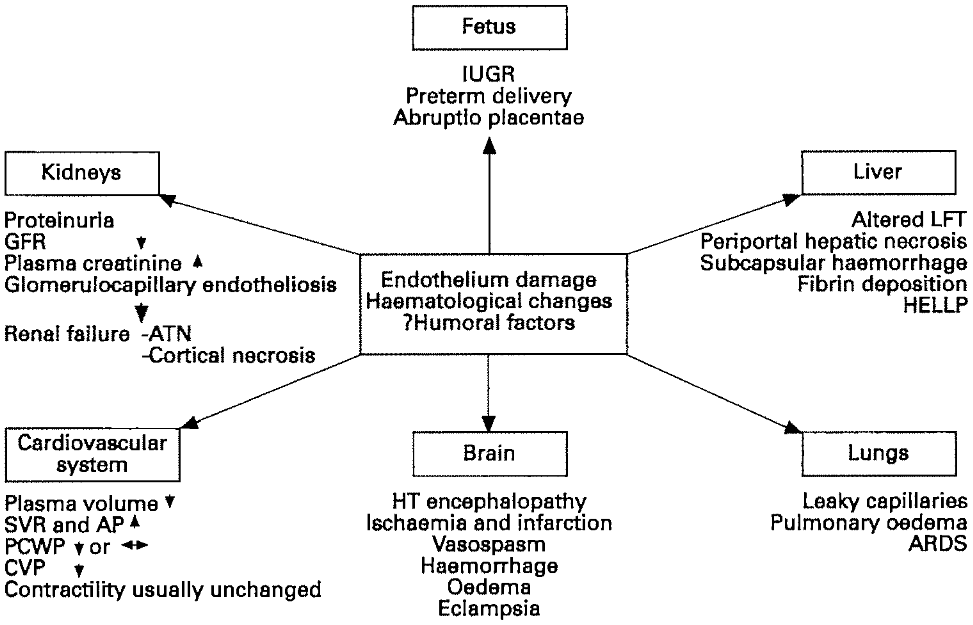


Figure 2 Multisystem changes occurring in pre-eclampsia. (GFR = glomerular filtration rate, ATN = acute tubular necrosis, SVR = systemic vascular resistance, AP = arterial pressure, PCWP = pulmonary capillary wedge pressure, CVP = central venous pressure, IUGR = intrauterine growth retardation, HT = hypertensive, LFT = liver function test, HELLP = haemolysis, elevated liver enzymes and low platelets, ARDS = adult respiratory distress syndrome.)

CARDIOVASCULAR SYSTEM

Hypertension is an early sign of pre-eclampsia and this may result partly from severe vasospasm. Typically, arterial pressure is unstable at rest and the circadian variation in arterial pressure variation is altered. Initially there is loss of the normal reduction in arterial pressure which occurs at night and subsequently, in severe cases, there is a reversed pattern with an increase in pressure during sleep. Responses to circulating adrenaline and noradrenaline are exaggerated. While normal pregnant women lose sensitivity to angiotensin II (which is a potent vasoconstrictor), patients with pre-eclampsia develop increased sensitivity to this hormone [39].

There have been a huge number of studies of the haemodynamic state in pre-eclampsia using both non-invasive [46, 87, 140] and invasive [11, 30, 32, 54, 83) techniques. Comparison of the findings of these studies is not easy because of large variation in patient population, severity of pre-eclampsia, type of therapy used for treatment, the stage of pregnancy or labour and the presence of concomitant medical disease such as chronic hypertension. In untreated patients with severe pre-eclampsia, studied with invasive monitoring [11, 32] it was found that cardiac index (CI) was either low or normal, systemic vascular resistance (SVR) was either normal or very high and pulmonary capillary wedge pressure (PCWP) was either low or normal. In treated patients [11, 32, 83] CI, SVR and PCWP were found to be normal to high. In women with severe pre-eclampsia, there is significant disparity between central venous pressure (CVP) and PCWP [32, 83].

There are several reports of reduced plasma volume in patients with pre-eclampsia as may be expected from the foregoing. In a review by Chelsey [21] it was suggested that the average plasma volume in pre-eclamptic women was 9 % lower than that of normotensive women and 30–40 % lower in patients with severe disease. However Sibai and colleagues [120] found that the plasma volume was normal in patients with mild disease. It is generally accepted that the decrease in the plasma volume is more obvious clinically in patients with severe disease.

In severe pre-eclampsia, plasma albumin is reduced as a result of loss in urine and loss across the leaky capillaries; consequently, colloid osmotic pressure (COP) is reduced [13]. Oian and colleagues [95] studied COP in patients with moderate and severe pre-eclampsia and found values of 20 mm Hg and 15 mm Hg in moderate and severe pre-eclampsia respectively compared with COP of 22 mm Hg in normotensive patients at term [13]. After delivery COP normally decreases as a result of fluid shift; typically in normotensive patients at 16–18 h post-delivery COP may be of the order of 16.2 mm Hg while in pre-eclamptic patients at this time, COP was as low as 13.8 mm Hg [146].

RESPIRATORY

Pulmonary oedema is not uncommon in pre-eclampsia. Sibai [123] found an incidence of 2.9 % in patients with pre-eclampsia and eclampsia; 70 % of the cases developed pulmonary oedema 71 h after delivery. It occurred more commonly in association with multiple organ dysfunction than as an isolated complication.

Pulmonary oedema occurs as a result of (a) a low COP in association with increased intravascular hydrostatic pressure, and (b) increased capillary permeability [14].

Colloid osmotic pressure and intravascular hydrostatic pressure

The colloid osmotic pressure (COP) is the pressure acting to prevent the movement of fluid out of the capillaries and the pulmonary capillary wedge pressure (PCWP) is a measure of the hydrostatic pressure operating in the opposite direction. Rackow and colleagues [99] studied 17 non-pregnant, critically ill patients with non-cardiogenic pulmonary oedema and found that a COP-PCWP difference of 4 mm Hg or less was always associated with pulmonary oedema. The COP in pre-eclamptic patients is lower than that in normotensive mothers [13] and typical pre-delivery/pre-treatment values of COP have been reported to range from 20 mm Hg in moderate pre-eclampsia to 15 mm Hg in severe pre-eclampsia [95] while PCWP values of > 12 mm Hg were found in 30 % treated patients with pre-eclampsia [32]. Increased hydrostatic pressure in pulmonary capillaries may occur as a result of left ventricular dysfunction, iatrogenic fluid overload and postpartum mobilization of extravascular fluid. In a group of women studied by Benedetti and colleagues [14], the most common cause of pulmonary oedema was alteration in hydrostatic-oncotic forces that occurred within 15 h postpartum and no patient had left ventricular dysfunction. The increase in PCWP in these patients (mean 18.6 mm Hg) was caused by mobilization of fluid from the extravascular to the intravascular compartment that normally occurs after delivery and also the effects of administering fluid with strong osmotic effects [14]. The use of colloids without adequate monitoring may increase the risk of pulmonary oedema.

Capillary permeability

The second most common cause of pulmonary oedema found in Benedetti's study was altered pulmonary permeability. The pathology underlying increased capillary permeability is not clear but it is probably endothelial cell damage. In this situation pulmonary oedema may be precipitated by acute fluid administration, amniotic fluid emboli or sepsis [4] and this may lead to adult respiratory distress syndrome (ARDS).

CENTRAL NERVOUS SYSTEM

The pathogenesis of eclampsia continues to be the subject of extensive investigations and speculation. The mechanisms suggested include vasospasm, ischaemia, haemorrhage, hypertensive encephalopathy, disseminated intravascular coagulation (DIC) and cerebral oedema [9]. Although the cerebral pathology of eclampsia resembles that of hypertensive encephalopathy with thrombosis, fibrinoid necrosis of cerebral arterioles, diffuse microinfarcts and petechial haemorrhages [23, 116], clearly hypertensive encephalopathy alone cannot account for all the central nervous system complications. While retinal haemorrhages, exudates and papilloedema are hallmarks of hypertensive encephalopathy, these changes are rarely encountered in eclamptics. In addition, at least 20 % of eclamptics do not have a systolic arterial pressure of > 140 mm Hg or a diastolic pressure of more than 90 mm Hg [51].

Magnesium sulphate, a known cerebral vasodilator, controls eclamptic convulsions very effectively and this lends support to the aetiology of cerebral vasospasm. Cerebral oedema was thought to be present in 20 % of patients dying with pre-eclampsia [80]. Diffuse cerebral oedema [69], haemorrhages [89] and infarcts [52] have been demonstrated in patients with eclampsia using computed tomography (CT) scanning. Most recently, magnetic resonance image (MRI) studies of brains of eclamptic women revealed focal changes characteristic of ischaemia [115]. Although the mechanism of convulsions is still controversial, it is likely that the aetiology depends on an interplay between vasospasm, microinfarcts and oedema.

Abnormal EEGs are frequent in pre-eclampsia [127]. The EEG pattern is usually a diffuse slow activity (theta or delta waves) sometimes with focal slow activity or paroxysmal spike activity but these are not pathognomic of pre-eclampsia as similar patterns are found in other conditions [127]. EEG abnormalities were thought to be related directly to the severity of maternal hypertension and may have explained claims that convulsions are secondary to cortical lesions developing after sudden increase in arterial pressure [44]. However Sibai and colleagues did not find any correlation between the degree of maternal arterial pressure elevation and the presence of EEG abnormality [127]. Hence a relationship between eclamptic convulsions and degree of maternal hypertension is questionable.

Visual disturbances in the form of photophobia, diplopia, scotomata, amaurosis or blurred vision are not uncommon in pre-eclampsia. Ischaemia caused by vasospasm of the posterior cerebral arteries or cerebral oedema in the occipital regions may be the cause of these visual disturbances [35].

Other neurological complications of pre-eclampsia include headache, hyperreflexia and clonus which are warning signs of increased cerebral irritation. Headache can occur in 40% of patients with pre-eclampsia and 80% of women who subsequently develop eclampsia [124]. Headache may be associated with nausea, excitability, apprehension and visual disturbances [119].

RENAL

The type of proteinuria in pre-eclampsia is non-selective; the increased permeability allows proportionally more larger molecular weight proteins such as transferrin and globulins to appear in the urine than occurs in renal disease with selective proteinuria [92]. The majority of women with pre-eclampsia have mild to moderately diminished renal perfusion and glomerular filtration with correspondingly elevated serum creatinine concentration. The decrease in glomerular filtration is caused partly by the glomerular swelling, narrowing of the glomerular capillary lumen and fibrin deposition in the endothelial cells (glomerular capillary endotheliosis). Although oliguria is common (i.e. urine output of < 20–30 ml h^{-1} over 2 h), progression to renal failure is rare. Acute tubular necrosis is often the cause of the reversible renal failure and this has a good prognosis [129]. Abruptio placentae, DIC and hypovolaemia usually precede the renal failure. Cortical necrosis, which is fortunately uncommon, causes permanent renal failure.

The renin-angiotensin-aldosterone system (RAAS) always seemed to provide a logical mechanism for the development of hypertension in pregnancy. Patients with pre-eclampsia have an increased response to angiotensin II [39]. However, this abnormal pressor response has been shown to be increased significantly by 22 weeks' gestation in patients who later develop pre-eclampsia. Despite extensive research, the role of the RAAS in pre-eclampsia is still unclear.

COAGULATION

Thrombocytopenia is a common finding in pre-eclampsia occurring in one-third of all patients [68]. Fortunately significant thrombocytopenia ($< 100 \times 10^9$ litre^{-1}) occurs in only 15% of women with severe disease [97]. This is caused by increased platelet consumption associated with low grade DIC [7]. Platelet activation is suggested by the findings of an inverse relationship between platelet count and fibrinogen degradation products, increased platelet specific protein β-thromboglobulin [7], and reduced platelet content of 5-hydroxytryptamine (5-HT). The thrombocytopenia is also thought to involve autoimmune mechanisms as evidenced by increased platelet associated immunoglobulin G levels. The effect of this thrombocytopenia on bleeding is not clear. Schindler [114] was unable to demonstrate a prolongation in bleeding time in patients with platelet counts below 100×10^9 litre^{-1}. However, other workers [104] reported a significant number of women with severe pre-eclampsia who had prolonged bleeding times despite an adequate platelet count. They showed that there was a good correlation between bleeding time and platelet count only when platelet count was lower than 100×10^9 litre^{-1}.

Table 5 The Collaborative Trial of Low Dose Aspirin [28]

Aim To investigate benefits of low dose aspirin (60 mg) and any fetal/neonatal or maternal side effects

Study

Multicentre

Large study (9634 patients)

Randomized, double blind and controlled

Results

	Aspirin	*Placebo*	*Significance*
Incidence of pre-eclampsia	6.7%	7.6%	ns
Birth weight (SD)	3024 (788)	2991 (810)	ns
Stillbirths/neonatal deaths	2.7%	2.8%	ns
Total neonatal mortality	4.3%	4.7%	ns
Preterm delivery	19.7%	22.2%	ns
Placental abruption	1.8%	1.5%	ns
Blood transfusion (mother)	4.0%	3.2%	S
Neonatal intraventricular haemorrhage	0.7%	0.9%	ns
Maternal deaths	3	1	ns

Conclusions

1. Routine prophylactic or therapeutic use of antiplatelet therapy for all women at risk of developing pre-eclampsia or IUGR is not recommended.
2. There is a small risk of increased peripartum haemorrhage.
3. Groups of patients who benefit: history of early onset pre-eclampsia and preterm delivery.
4. No increased neonatal morbidity or mortality.
5. No increased maternal mortality.

Maternal vascular prostacyclin is reduced in pre-eclampsia and platelet thromboxane A_2 production is increased. The resulting imbalance between prostacyclin and thromboxane is likely to contribute to the enhanced platelet activity and vascular damage. Aspirin inhibits cyclo-oxygenase, which is required for prostaglandin and thromboxane production, and therefore it reduces thromboxane generation and platelet activation. Aspirin also inhibits vascular prostacyclin production and this action may not be beneficial. However when given in low dose, aspirin may have selective actions and only block thromboxane production without affecting systemic vascular prostacyclin production because of lower concentrations of the drug in the systemic circulation compared with the portal circulation, the site of thromboxane inactivation. In addition, the nucleated vascular endothelial cells, unlike anucleated platelets, can synthesize new proteins and are therefore able to replace the inactivated thromboxane [56]. This provided the rationale for aspirin prophylaxis (table 5). The mechanism underlying prostacyclin deficiency is unclear.

In patients with mild pre-eclampsia, there are very small changes in the coagulation system detectable only by sensitive tests. Increased levels of fibrinopeptide, factor VIIIc activity, von Willebrand factor levels and reduced antithrombin III suggest activation of the coagulation cascade. Haemolysis may occur especially in association with abnormal liver function; these changes occur in the HELLP syndrome [143]. DIC occurs in 7 % of cases of severe pre-eclampsia or eclampsia [126] but the underlying cause is unclear.

HEPATIC

Pathological changes have been described by Sheehan and Lynch [116] in the livers of women dying of pre-eclampsia or eclampsia. The impaired liver function in severe pre-eclampsia can affect clearance of drugs metabolised by the liver. The cause of the hepatic dysfunction is not clear but it may result from periportal hepatic necrosis, subcapsular haemorrhages or fibrin deposition in hepatic sinusoids [6]. Spontaneous liver rupture is a rare but potentially lethal complication which carries a 60 % mortality [78]. Abnormal liver function tests may be part of the HELLP syndrome.

FETUS

Impairment of placental perfusion caused by placental disease and vasospasm is almost certainly the major reason for the high incidence of fetal loss, intrauterine growth retardation (IUGR), small-for-dates infants and perinatal mortality. In addition, the state of the mother frequently necessitates early termination of pregnancy and consequently, the incidence of respiratory distress syndrome is higher in neonates born to mothers with pre-eclampsia. Placental abruption is more common in pre-eclamptics [133] and is associated with a high perinatal mortality. It has also been found that there is a shift of the oxyhaemoglobin curve to the left in these patients and this decreases oxygen availability to the fetus [67].

Prediction of pre-eclampsia

Pre-eclampsia is the most important cause of maternal mortality in developed countries. Therefore, the prevention of pregnancy-induced hypertension is important for the sake of both mother and child. Prevention assumes both the ability to predict hypertension early enough to intervene and the existence of effective interventions. Without a practical early predictor, interventions cannot be developed.

During the past two decades more than 100 clinical, biophysical and biochemical tests have been reported in the literature to predict the development of pre-eclampsia [41]. However, the results of most studies have been inconsistent and contradictory. Currently, there is no ideal predictive test that fulfils all desired criteria.

The two most important predictive factors remain nulliparity and family history. Pre-eclampsia is present in 5.8 % of primigravidas but only 0.4 % of secundagravidas [84]. There is considerable evidence to support a significant genetic contribution to pre-eclampsia [29]. While several reports have established the likelihood of a recessive gene trait acting in pre-eclampsia, recent evidence on discordance among identical twins suggests that a single gene involvement is unlikely [139].

Arterial pressure in the second trimester and pressor tests have been investigated in the prediction of pre-eclampsia but there is such a large reported variation in their sensitivity and specificity as to render them of no predictive value.

Concentrations of a large number of constituents of blood and urine have been shown to change in pre-eclampsia including a high haemoglobin at first antenatal booking, elevated factor VIII-related antigen, reduced antithrombin III concentration, low platelet count and platelet AII binding. However, their proposals as predictors of pre-eclampsia have proved disappointing.

Doppler ultrasound studies of the deep lying arcuate arteries at 16–18 weeks' gestation may diagnose impaired trophoblastic invasion of the spiral arteries and may have potential in predicting pregnancies destined to become complicated by pre-eclampsia [134].

Prevention

The aetiology and pathophysiology of pre-eclampsia are still not understood fully and this has hindered development of effective preventive measures. So far, preventive strategies have concentrated on areas thought to be involved in the pathogenesis of pre-eclampsia, i.e. endothelium and prostaglandins.

ANTI-PLATELET THERAPY

Platelets appear to play a significant role in pathogenesis of pre-eclampsia and early small-scale studies suggested that aspirin may be effective in preventing pre-eclampsia [60] especially in reducing the more severe complications of intrauterine growth retardation and the risk of pregnancy-induced hypertension, with no observed risk of neonatal and maternal adverse effects. However these benefits were not consistently observed in other studies [62, 121]. Unfortunately, these studies were not large enough to provide definite evidence as to the safety and efficacy of prophylactic aspirin during pregnancy. The recent Collaborative Low Dose Aspirin study (CLASP) [28] was designed to overcome the weakness of previous studies. This was a large multicentre trial (table 5). The results were disappointing in that aspirin did not affect significantly the incidence of proteinuria, eclampsia, IUGR, stillbirths or neonatal deaths. The use of aspirin was associated with a reduction of only 12 % in the incidence of pre-eclampsia which was not significant. It was concluded that the routine prophylactic use of aspirin or antiplatelet treatment in all women who are at risk of developing pre-eclampsia is not justified. Low dose aspirin may be justified only in women thought to be especially liable to early onset pre-eclampsia severe enough to need preterm delivery. In such women, it seems appropriate to start low dose aspirin in the second trimester. The use of aspirin was associated with increased requirement for postpartum blood transfusion [28] and a higher incidence of abruptio placentae [121].

MAGNESIUM AND ZINC

Although magnesium supplementation has been suggested as a possible means of reducing the incidence of pre-eclampsia [132] clinical trials have yielded conflicting results [15, 132] and the current recommended daily allowance of 320 mg per day should not be exceeded. Zinc has also been studied but there are no convincing data for any efficacy.

FISH OILS

Fish oils are a source of long chain n-3 unsaturated fatty acids that yield eicosapentaenoic acid for the synthesis of thromboxane A_3 and prostacyclin I_3 instead of thromboxane A_2 and prostacyclin I_2 derived from arachidonic acid. These substances therefore shift the balance of platelet reactivity towards inhibition of aggregation and increased vasodilatation [107]. However, large controlled multicentre trials need to be organized to assess any beneficial or negative effects of fish oil supplementation in pregnancy.

CALCIUM

There is an inverse relationship between calcium intake and hypertensive disorders of pregnancy [12] and until recently it was thought that calcium supplements cause a significant reduction in the incidence of gestational hypertension but not pre-eclampsia itself. However, more recent studies have demonstrated that calcium supplements reduced the incidence of hypertension, pre-eclampsia and preterm delivery [18, 141]. Again controlled trials are needed to confirm if there is any significant reduction in perinatal mortality in order to recommend routine use of calcium supplements during all pregnancies.

REPEATED EXPOSURE TO SPERM

Recently, Robilhand [109] has reported data from a prospective study suggesting that pre-eclampsia may be prevented by increasing the duration of sexual cohabitation before the first pregnancy with that partner. The overall incidence of pregnancy-induced hypertension in their study decreased from 10.6 % in the general population to 5.1 % in women with more than 12 months' cohabitation before conception. They suggested that protection may be induced by an immune response in the female to repeated exposure to antigens on the sperm.

Treatment

In the absence of complete understanding of the pathogenesis of the syndrome, management is based mainly on treatment of symptoms and signs of the secondary effects of pre-eclampsia and it is designed to reduce maternal and fetal complications. The management of these patients should ideally be multidisciplinary and the anaesthetist should be involved in the care of patients with severe pre-eclampsia at an early stage. In addition to deciding when (table 6) and how to deliver, management should include treatment of hypertension, oliguria and fluid therapy, coagulation abnormalities and convulsions.

Table 6 Severe pregnancy-induced hypertension—indications for delivery (DIC = disseminated intravascular coagulation, IUGR = intrauterine growth retardation)

1. Patient at term or at a gestation where viability of the fetus is not a concern
2. At any stage of pregnancy for:
    - Maternal complications such as:
        - renal failure
        - hepatic disorder
        - falling platelets or DIC
        - HELLP syndrome
        - eclampsia
    - Fetal complications
        - chronic fetal compromise:
            - IUGR
            - Oligohydramnios
            - Doppler abnormalities
        - acute fetal compromise
            - Cardiotocographic abnormalities
            - Placental abruption

TREATMENT OF HYPERTENSION

Cerebral haemorrhage is a major cause of maternal deaths (60 %) from pre-eclampsia or eclampsia [42]. When mean arterial pressure (MAP) exceeds 140 mm Hg (equivalent to 180/120), there is a significant risk of maternal cerebral vascular accident (CVA) [90]. Therefore, it is recommended that arterial pressures of greater than 170/110 should be treated with urgency with the aim of maintaining pressure below 170/110 but above 130/90. The aim should be to prevent intracerebral haemorrhage while not affecting uteroplacental blood flow and maternal renal function. Precipitous reductions in arterial pressure should be avoided by adequate volume expansion before the use of vasodilators. Prolonged treatment of hypertension is advisable when the fetus is immature in an attempt to delay delivery to allow further maturation. However, this can only be undertaken provided the mother is not placed at increased risk and that strict monitoring of both the mother and the fetus is carried out at frequent regular intervals. Hospitalization and bed rest may be all that are required in some patients but it has been suggested that this has little effect on arterial pressure [47].

Prolonged therapy

Many antihypertensive drugs have been used including methyldopa, β-blockers and nifedipine. ACE inhibitors are associated with toxic effects in the fetus in both animals and humans [55] and are therefore contraindicated.

Methyldopa, a centrally acting drug which reduces sympathetic outflow, is effective in maintaining arterial pressure at a safe level in the majority of women with pre-eclampsia [90] and in reducing the frequency of severe hypertensive episodes. However, because pre-eclampsia is a progressive disorder, methyldopa may eventually fail to provide adequate control. In this situation, another antihypertensive may be used and plans made for the delivery of the baby. Methyldopa is the only antihypertensive drug with documented long-term safety for the newborn. It is usually given in an initial dose of 1 g day^{-1} in three to four divided doses and may be increased to 3 to 4 g day^{-1}. Methyldopa appears to reduce the small risk of mid-trimester abortions seen in association with early hypertension.

Labetalol has theoretical advantages particularly for the uteroplacental vasculature because of its α-blocking properties. It provides adequate control of arterial pressure but long-term fetal/neonatal effects have not yet been evaluated adequately. There is concern that β-blockers may impair the capacity of the fetus to cope with intrauterine stress. In one trial [17] atenolol was associated with growth retardation when started early in pregnancy for essential hypertension. Clinical studies on the chronic administration of nifedipine in pregnancy are limited. Nifedipine given either as first line treatment [61] or as second line treatment [76] was effective in controlling arterial pressure in most patients. However, there are limited data on its effects on the fetus or neonate.

Acute therapy

A large number of agents have been used for acute control of arterial pressure but hydralazine is the most widely used agent. Its main advantage is the extensive experience of its use. It may be given either as intermittent bolus doses (5–10 mg every 20 min) or as a continuous infusion (5–20 mg h^{-1}) following an initial 5 mg bolus [90]. The onset of action of hydralazine is 20–30 min; this must be appreciated because if sufficient time is not allowed between injections, hypotension can occur. One of the drawbacks of hydralazine is that its side effects (headache, tremor and vomiting) mimic the symptoms of impending eclampsia.

Labetalol is a combined α- and β-blocking agent, with a relatively rapid onset of action causing maximal effects within 20 min after 50 mg i.v. bolus or 30 min after 100 mg administered orally. These boluses may be repeated at intervals of 20 to 30 min as necessary. Labetalol may also be given as a continuous infusion at 20 to 160 mg h^{-1}. Labetalol appears to be a satisfactory alternative to hydralazine and it may be preferable because of relative freedom from maternal side effects. However, there is less experience with its use particularly in relation to effects on the fetus and neonate. It is also contraindicated in asthmatic patients. Hypotension, oliguria and bradycardia have been reported occasionally in neonates when the drug was given in the presence of fetal distress or hypoxia [144]. The use of β-blockers in severe pre-eclampsia impairs the capacity of the fetus to cope with intrauterine stress and it may attenuate the usual signs of fetal distress.

Nifedipine is used widely for the management of acute and chronic hypertensive non-obstetric patients. Although it is unlicensed for use in pregnancy [86] it has been shown to be satisfactory in the management of hypertension in pregnancy [76]. Experience with its use is limited and it requires further careful monitoring. Two oral preparations of nifedipine are available which act rapidly; nifedipine capsules within 10–15 min and nifedipine slow release tablets within 45 to 60 min with a more prolonged effect. Nifedipine has also been given sublingually; a dose of 5 mg was found to maintain uteroplacental blood flow despite a reduction in arterial pressure and uterine perfusion pressure [77]. In this study, pregnancy outcome was not discussed, but there was no evidence of fetal distress. Nifedipine should be used with caution if magnesium sulphate ($MgSO_4$) is being given concurrently as potentiation may occur leading to profound hypotension [142].

Other antihypertensives which are used less frequently include diazoxide, sodium nitroprusside (SNP) and glyceryl trinitrate (GTN). Their hypotensive effects occur rapidly and there is a considerable risk of excessive hypotension and reduced uteraplacental blood flow. GTN is administered as a continuous infusion at an initial rate of 10 μg min^{-1} and titrated against response. There is a risk of methaemoglobinaemia if a dose of 7 μg kg^{-1} min^{-1} is exceeded. SNP is given at an initial rate of 0.25 μg kg^{-1} min^{-1} and increased according to response. Worries about fetal cyanide toxicity and death observed in previous animal studies discouraged its use, but more recent studies have failed to reveal evidence of cyanide accumulation in the fetus [49]. Direct arterial pressure measurement is recommended whenever GTN or SNP is used.

FLUID THERAPY

Pre-eclampsia is associated with a reduction in intravascular volume, haemoconcentration and hypoproteinaemia but pulmonary oedema occurs in some cases of pre-eclampsia and therefore there is some controversy on optimum fluid therapy.

It is generally accepted that plasma volume should be corrected by volume expanders before vasodilatation with either drugs or extradural analgesia/anaesthesia. Hypotension and fetal distress were reported in patients who had extradural analgesia or hydralazine without appropriate fluid therapy [20]. The question therefore is often not whether to give fluid but what type, how much, how rapidly and with what level of monitoring.

The crystalloid–colloid controversy is still debated in the management of pre-eclamptic patients because the condition is complicated by both low COP and leaky capillaries and they are therefore at risk of developing non-cardiogenic pulmonary oedema [123]. Administration of colloid solution may increase COP transiently but there is no evidence to suggest that this improves clinical outcome. Crystalloids may be given instead at a rate of 1–2 ml kg^{-1} h^{-1} and altering subsequent fluid therapy according to the patient's clinical condition and urine output in addition to CVP and PAWP measurements where necessary. Infusion of crystalloid alone decreases oncotic pressure further [146], while the use of colloid such as albumin may result in high CVP and PAWP values and the onset of pulmonary oedema particularly in the postpartum period [71]. If pulmonary oedema develops, it requires treatment by conventional medical therapy including oxygen, diuretics, reduction in preload/afterload, fluid restriction and intermittent positive pressure ventilation.

It is not clear what constitutes ideal CVS monitoring of patients with pre-eclampsia but one can safely state that the level of monitoring required should be tailored to each patient. Joyce and colleagues [66] evaluated the effects of fluid loading in pre-eclampsia patients with a low CVP (-1 to -4 cm H_2O) before extradural block. They found it necessary to give 750 ml plasmanate and 2 litre Ringer lactate in order to achieve CVP values of $+6$ cm H_2O. This regimen was associated with a high postpartum CVP (16–18 cm H_2O) and several cases of pulmonary oedema. It is now recognized that on occasions there may be a poor correlation between CVP and left atrial pressures [32]. Benedetti and colleagues [14] found no correlation between CVP and PCWP when the CVP exceeded > 6 mm Hg. Common indications for a CVP catheter include oliguria, impending or established pulmonary oedema and signs of severe pre-eclampsia. Because these patients may have a coagulation abnormality, it may be preferable to insert a central venous catheter via a peripheral site such as the antecubital fossa.

Insertion of a pulmonary artery catheter allows measurement of PCWP, CO and SVR. In severe pre-eclampsia PCWP is usually normal or low and in this situation, with good left ventricular function and high SVR, infusion of fluids allows the use of vasodilators and improves renal output [26]. However, if the PCWP is high with or without poor LV function, volume therapy may need to be carefully controlled. Insertion of a PAP catheter is associated with maternal morbidity and mortality [20] especially in these patients who may have coagulation abnormalities. Criteria recently proposed for pulmonary artery (PA) catheterization in patients with severe pre-eclampsia [27] include: patients failing to respond to antihypertensive treatment, pulmonary oedema, unresponsive oliguria and where extradural anaesthesia is contemplated. Many experts believe that these criteria are too broad and that there are few indications for a PA rather than a CVP catheter.

TREATMENT OF OLIGURIA

The pathogenesis, definition and management of oliguria in severe pre-eclampsia is still not well defined. The definitions of oliguria used in clinical practice include a urine output of < 30 m h^{-1} for 3 h, < 30 ml h^{-1} for 2 h, < 0.5 ml kg^{-1} h^{-1} for 2 h, < 500 ml 24 h^{-1} or < 100 ml 4 h^{-1}. The diagnosis of oliguria should be based on at least a 4-h period. Many patients with a transient decrease in urine output to < 30 ml h^{-1} often resume normal urine output spontaneously without any therapy [122]. Poor renal function in these patients has a good prognosis [129].

The oliguric patient may be treated with a fluid challenge of 500 to 1000 ml crystalloid. Lee and colleagues [73] showed in seven patients that oliguria was a poor index of volume status in patients with pre-eclampsia. If there is no response to a fluid challenge, the CVP should be monitored in the knowledge that this does not always correlate with PCWP when CVP is > 6 mm Hg [14]. Repetitive unmonitored fluid administration should be avoided as this may lead to pulmonary oedema especially in the postpartum period [14].

The use of dopamine in pre-eclampsia has not been widely investigated. Kirshon and colleagues [70] studied the effects of low dose dopamine (1–5 μg kg^{-1} min^{-1}) in six oliguric patients. Cardiac output increased from 6.8 (SD 1.8) to 8.0 (2.3) litre min^{-1}, while arterial pressure, CVP and PCWP did not change significantly. Urine output increased from 21 (10) to 43 (23) ml h^{-1} and there were no adverse maternal or fetal side effects.

Nifedipine 10 mg orally every 4 h has been shown to increase urine output significantly in the postpartum period [8]. Although the mechanism of action is unknown, it may be related to increased renal blood flow.

MANAGEMENT OF ECLAMPSIA

Because the pathogenesis of eclamptic convulsions is still poorly understood it is not surprisingly that there is disagreement on how to treat the condition. In the past, most clinicians agreed that diazepam was appropriate but this view has been challenged recently [137]. Chlormethiazole has become less popular because of the need to administer large volumes of fluid and because of the ease of oversedation with loss of airway reflexes. Phenytoin achieved popularity because of lack of sedative side effects and it has been the agent of choice in the UK.

Table 7 The Collaborative Eclampsia Trial [137]. Comparison of magnesium sulphate (M), diazepam (D) and phenytoin (P) in the treatment of eclampsia. S = significant, NS = non-significant differences.

Aim To compare $MgSO_4$, diazepam and phenytoin in the treatment of eclampsia

Study Multicentre, randomized, large (1680 patients)

Results	*M* (%)	*D* (%)	*S*	*M* (%)	*P* (%)	*S*
Recurrent fits	13.2	27.9	S	5.7	17.1	S
Maternal mortality	3.8	5.1	NS	2.6	5.2	NS
Perinatal mortality	24.8	22.4	NS	26.1	30.7	NS
Ventilation	5.5	6.0	NS	14.9	22.5	S
Respiratory Depression	7.7	7.3	NS	8.2	11.6	NS
Pneumonia	2.0	3.1	NS	3.9	8.8	S
ITU admissions	14.3	16.6	NS	16.7	25.1	S
Blood transfusions	15.1	20.1	NS	19.7	27.0	S
Neonatal intubations	11.3	15.7	NS	12.7	23.9	S
SCABU admissions	46.5	50.2	NS	31.7	43.6	S

Conclusions

1. $MgSO_4$ should be the drug of choice for eclampsia
2. Phenytoin caused more maternal and neonatal morbidity
3. Diazepam and phenytoin had more recurrent convulsions compared with $MgSO_4$

Table 8 Use of $MgSO_4$ in eclampsia

Loading dose
  i.m. 4 g i.v. plus 5 g i.m. in each buttock
  i.v. 4–6 g i.v.
Maintenance
  i.m. 5 g i.m. every 4 h
  i.v. 1–2 g h^{-1} infusion
Toxicity
  4.0–6.5 mmol $litre^{-1}$
    nausea and vomiting
    somnolence
    double vision
    slurred speech
    loss of patellar reflex
  6.5–7.5 mmol $litre^{-1}$
    muscle paralysis
    respiratory arrest
  > 10 mmol $litre^{-1}$
    cardiac arrest

Magnesium sulphate was first suggested in 1906 and has been the main choice in the USA for over 60 years [117] and also in South Africa. However, until very recently, there had been little controlled evidence on the choice of anticonvulsants. Many previous studies were either too small or inconclusive [33, 43].

In the recent collaborative eclampsia trial [137], mothers allocated to receive $MgSO_4$ had a significant lower risk of recurrent convulsions than those allocated to either diazepam or phenytoin (table 7). Maternal mortality was lower (although non-significantly) among women who received $MgSO_4$ and in this group they were less likely to be admitted to ITU, less likely to undergo ventilation or have chest infections compared with the phenytoin group but there was no difference compared with the diazepam group. This large randomized and controlled multicentre study may be the turning point for the use of $MgSO_4$ in eclampsia in the UK.

$MgSO_4$ is not an anticonvulsant and its mode of action is not clearly understood. It is thought to reverse cerebral vasoconstriction [10], by blocking calcium influx through the NMDA (*N*-methyl-D-aspartate) subtype of glutamate channel [31]. $MgSO_4$ is given either i.v. or i.m. and the aim is to achieve a therapeutic concentration of 2–3.5 mmol $litre^{-1}$ [24] (table 8). Plasma concentrations exceeding 4 mmol $litre^{-1}$ cause toxicity which may be treated with i.v. calcium gluconate 1 g. Patients with poor renal function require a slower rate of infusion of $MgSO_4$ and closer monitoring of the patient for any signs of toxicity. When using $MgSO_4$, monitoring of the patients should include regular measurements of plasma concentrations of magnesium and assessment of tendon reflexes for hyporeflexia.

Are prophylactic anticonvulsants indicated?

Eclampsia occurs in women with established pre-eclampsia but in 38 % of cases, it occurs with no earlier warning. Predicting if an individual woman will develop eclampsia is difficult and this has contributed to the wide variation in the use of prophylactic anticonvulsants. The problem of prediction has been obviated in some units by treating all women with advanced pre-eclampsia with anticonvulsants. However, this is considered undesirable because it greatly increases the risks of major side effects. Chua and Redman have suggest that treatment should be reserved for those who have had their first convulsion [25]: 99 % of the units in USA use prophylactic $MgSO_4$ in all women with pre-eclampsia in labour [19]. Some units reserve prophylactic anticonvulsants for patients with impending eclampsia (visual disturbances, headache, increased reflexes and clonus). In the UK, 16 % of units do not prescribe prophylactic anticonvulsants [59]. Prophylactic anticonvulsants are only worthwhile if the benefit outweighs the harm from the side effects. There are few studies which have investigated prophylactic use of anticonvulsants in pre-eclampsia. Some studies comparing $MgSO_4$ with phenytoin [5, 81] had conflicting results. Studies comparing $MgSO_4$ with no treatment were too small to provide any conclusions [10, 22]. Therefore the debate on the benefit of prophylactic anticonvulsants will continue until large randomized studies comparing $MgSO_4$ and placebo are carried out.

HELLP syndrome

Pritchard and colleagues [98] first described an association of coagulation and liver enzyme abnormalities with pre-eclampsia in 1954 and Weinstein in 1982 coined the term HELLP [143] (haemolysis, elevated liver enzymes and low platelets).

The HELLP syndrome complicates 0.3 % of all pregnancies and between 4 and 20 % of those with severe pre-eclampsia [125, 138]. Maternal and fetal outcomes are poor with maternal mortality of up to 24 % and perinatal mortality of 33 % [128]. Thirty per cent of the cases occur in the postpartum period [125]. The clinical signs and symptoms include epigastric pain, upper abdominal tenderness, proteinuria, hypertension, jaundice, nausea and vomiting. The disease may progress to haematuria, oliguria, acute tubular necrosis, cortical necrosis and panhypopituitarism. Complications of HELLP syndrome are summarized in table 9. Laboratory investigations reveal thrombocytopenia, abnormal liver function tests, elevated plasma concentrations of haptoglobin and haemolytic anaemia. Sibai [125] suggested that the following standardized laboratory values be used to diagnose HELLP syndrome: (1) haemolysis, defined by abnormal peripheral blood smear, (2) increased bilirubin ($\geqslant$ 1.2 mg dl^{-1}) or increased lactate dehydrogenase ($\geqslant$ 600 u. $litre^{-1}$),

Table 9 Complications of HELLP syndrome (n = 442) [125]

1.	Maternal mortality	1.1 %
2.	Disseminated intravascular coagulation	21 %
3.	Abruptio placentae	16 %
4.	Acute renal failure	7.7 %
5.	Pulmonary oedema	6.0 %
6.	Subcapsular liver haematoma	0.9 %
7.	Retinal detachment	0.9 %
8.	Laparotomies for intra-abdominal bleeding	2.0 %
9.	Pleural effusion	6.0 %
10.	Adult respiratory distress syndrome	1.0 %
11.	Cerebral oedema	1.0 %
12.	Transfusion of blood products	55 %

(3) increased serum aspartate aminotransferase ($\geqslant$ 70 u. litre^{-1}), (4) low platelets defined as platelet count $< 100 \times 10^9$ litre^{-1}. Aggressive treatment is necessary and delivery should be carried out by Caesarean section if necessary [119]. Vaginal delivery is not contraindicated [118] but fetal thrombocytopenia in 20% of cases may make this hazardous [138]. Platelet transfusion is recommended if the platelet count is $< 20 \times 10^9$ litre^{-1} for vaginal delivery and $< 50 \times 10^9$ litre^{-1} for Caesarean section [118]. A transfusion of fresh whole blood is recommended if the haemoglobin is less than 10 g dl^{-1}. The bladder should be catheterized to monitor hourly urine output. Central venous pressure monitoring is usually necessary preferably via a peripheral vein. The choice of anaesthetic technique depends on the condition of the patient and fetus. Regional techniques may be contraindicated because of coagulation disturbances. The drugs used should have minimal hepatic and renal metabolism. Blood glucose should be monitored as severe hypoglycaemia has been reported in the HELLP syndrome [48].

Anaesthesia and analgesia in patients with pre-eclampsia

Extradural analgesia is preferred by most anaesthetists for providing pain relief in labour and anaesthesia for operative delivery provided that there are no contraindications. Ramanathan [102], found that extradural anaesthesia was associated with smaller maternal haemodynamic and neuroendocrine stress responses during elective Caesarean section in women with severe pre-eclampsia compared with general anaesthesia. Extradural anaesthesia also avoided the transient neonatal depression seen after general anaesthesia. In another study in patients with severe pre-eclampsia, lumbar extradural analgesia was found to reduce MAP from 121.4 to 97.7 mm Hg without altering CI, PVR, CVP or PCWP [93]. Provided that the patient has been preloaded with fluid (crystalloid 500 ml), and that supine hypotension is avoided, extradural analgesia has been found to increase intervillous blood flow. Ephedrine is safe to use in these patients as it does not adversely affect uterine blood flow [32]. The choice of local anaesthetic does not seem to be critical as bupivacaine 0.25% and 0.5%, lignocaine 2% and chlorprocaine 2% have been used without adverse effects [1, 64, 101]. The pharmacokinetics of lignocaine in pre-eclampsia differ from those in normotensive patients; total body clearance is prolonged and resulting in higher blood concentrations [1], probably because of the impaired liver function. It is recommended that adrenaline is avoided as these patients have increased plasma catecholamine levels. When extradural analgesia is used for pain relief during labour a mixture of an opioid and a local anaesthetic administered as an infusion is preferred as this gives continuous pain relief and less hypotension compared with intermittent boluses of local anaesthetic.

Spinal anaesthesia is often discouraged in patients with pre-eclampsia because of the risk of severe hypotension. In a retrospective study by Hood and Boese [58] comparing extradural and spinal anaesthesia for elective Caesarean section in patients with severe pre-eclampsia, there was a slightly greater reduction in arterial pressure in women who received spinal anaesthesia. However, the authors remarked that the difference between the two groups was only nearly statistically significant ($P < 0.052$) and that spinal anaesthesia is not as unsafe as generally thought. However, this retrospective study involved only 34 patients in the extradural group and 14 in the spinal group. A larger prospective study would be required before spinal anaesthesia can be recommended as being safe for patients with pre-eclampsia.

Thrombocytopenia is common in patients with pre-eclampsia and this may contraindicate regional analgesia. However, there is considerable debate on the reliability of platelet count in predicting the risk of extradural haemorrhage. A platelet count of > 150–400×10^9 litre^{-1} is generally accepted as normal but this may not be true during pregnancy. Previous studies have shown platelet count of less than 150×10^9 litre^{-1} in 6.4% of randomly selected healthy pregnant women. The current belief that extradural analgesia is contraindicated in women whose platelet count is less than 100×10^9 litre^{-1} has no experimental supporting data. Bleeding time and thrombelastography are better measures of platelet function than platelet count and should be used when there is any doubt. The disadvantage of the bleeding time is that most laboratories offer this test during limited hours, there is a significant inter- and intra-technician variability and there is lack of controlled evidence indicating that the use of bleeding times avoids extradural or spinal bleeding [20]. Some units do not routinely order bleeding time unless the platelet count is less than 80×10^9 litre^{-1} or if there is clinical and laboratory evidence of coagulopathy [75]. Other workers recommend that an extradural should not be used if platelet count is less than 80×10^9 litre^{-1} [110]. However it is important to balance the risk of bleeding into the extradural space against the relative risk of general anaesthesia in these patients. Unfortunately, to date there is no single reliable test to indicate the risk of bleeding into the extradural space.

GENERAL ANAESTHESIA IN PATIENTS WITH PRE-ECLAMPSIA

Regional anaesthesia is undoubtedly safer for patients with pre-eclampsia but general anaesthesia may be necessary when fetal distress requires immediate delivery or on occasions when regional analgesia has either failed or is contraindicated. General anaesthesia in patients with pre-eclampsia presents risks to the mother and baby. The hazards of general anaesthesia include: (1) potentially difficult intubation, laryngeal oedema may not become apparent until laryngoscopy [16], (2) potential aspiration of gastric contents, (3) difficulties related to neuromuscular blockers, (4) pressor response to laryngoscopy and intubation, and (5) impaired intervillous blood supply [65].

PROBLEMS WITH INTUBATION

Laryngeal oedema is a rare but potentially serious complication of pre-eclampsia. It often occurs as part of the general oedema and facial swelling but occasionally it occurs with few warning signs. It is, therefore, necessary to be prepared for a difficult intubation in these patients, to have a wide range of size of tracheal tubes and to avoid repeated intubations as this may worsen the oedema. As laryngeal oedema may also develop during the intraoperative period [111], anaesthetists need to take care when extubating the tracheae of these patients. Before extubation, the cuff should be deflated and air passing the tracheal tube is assessed by occluding the tracheal lumen and allowing the patient to breathe around the tube as suggested by Potgieter and Hammond [96].

PRESSOR RESPONSE TO INTUBATION AND EXTUBATION

The pressor responses to laryngoscopy, intubation and extubation may increase the risks of cerebrovascular accidents, increase myocardial oxygen requirements, induce cardiac arrhythmias, induce pulmonary oedema and reduce uterine blood flow. Many drugs have been used in an attempt to attenuate these responses. Hydralazine is ineffective [100] while labetalol in doses up to 1 mg kg^{-1} (given in 10–20 mg boluses) has been shown to cause a moderate reduction in MAP and heart rate at intubation [103]. A newer β-blocker, esmolol, is currently under investigation; it has a rapid onset of action and shorter duration of action and may prove to be useful not only for intubation but also extubation. Short-acting opioids have also been used at induction of anaesthesia [36]. Although the neonate's condition at birth is generally an important consideration in choice of anaesthetic agent, in pre-eclampsia and eclampsia, the condition of the mother is always the anaesthetist's primary concern [57]. Fentanyl 2.5 μg kg^{-1} has been compared with alfentanil 10 μg kg^{-1}; while both drugs reduced the pressor response to intubation they did not abolish it [113] possibly as a result of inadequate dosage. Fentanyl 200 μg and droperidol 5 mg were found to obtund the hypertensive response to intubation [72], $MgSO_4$ has been used to control both catecholamine release and the pressor response [63]. It was found that pre-treatment with $MgSO_4$ 40 mg kg^{-1} appeared to be superior to either lignocaine or alfentanil [3]. Other drugs which have been used in this situation include lignocaine, SNP [135], GTN [79] and trimetaphan [131]. Calcium channel blockers such as nifedipine are currently being investigated.

PROBLEMS WITH NEUROMUSCULAR BLOCKERS

Where the mother has received $MgSO_4$, the non-depolarizing neuromuscular blockers are potentiated and they should be used with caution. $MgSO_4$ inhibits calcium facilitated pre-synaptic transmitter release hence enhancing sensitivity to non-depolarizing neuromuscular blockers [130]. Fasciculations may not occur after administration of suxamethonium to a mother treated with $MgSO_4$.

References

1. Abboud T, Artal R, Sarkis F, Henriksen EH, Kammula RK. Sympathoadrenal activity, maternal, fetal and neonatal responses after epidural anesthesia in the pre-eclamptic patient. *American Journal of Obstetrics and Gynecology* 1982; **144**: 915–918.
2. Ales KL, Noton ME, Druzin ML. Early prediction of antepartum hypertension. *Obstetrics and Gynecology* 1989; **73**: 928–933.
3. Allen RW, James MFM, Uys PC. Attenuation of the pressor response to intubation in hypertensive proteinuric pregnant patients by lignocaine, alfentanil and magnesium sulphate. *British Journal of Anaesthesia* 1991; **66**: 216–223.
4. Anderssen FH, Lynch JP, Johnson TRB. Adult respiratory distress syndrome in obstetrics and gynaecology. *Obstetrics and Gynecology* 1980; **55**: 291–295.
5. Appleton MP, Kuetie TJ, Raebel M. Magnesium sulphate versus phenytoin for seizure prophylaxis in pregnancy-induced hypertension. *American Journal of Obstetrics and Gynecology* 1991; **165**: 907–913.
6. Arias F, Mancilla-Jimenez R. Hepatic fibrinogen deposits in pre-eclampsia. Immunofluorescent evidence. *New England Journal of Medicine* 1976; **295**: 578–582.
7. Ballegeer VC, Spitz B, De Baene LA, Van Assche AF, Hidajat M, Criel AM. Platelet activation and vascular damage in gestational hypertension. *American Journal of Obstetrics and Gynecology* 1992; **166**: 629–633.
8. Barton JR, Hiett AK, Conover WB. The use of nifedipine during the postpartum period in patients with severe pre-eclampsia. *American Journal of Obstetrics and Gynecology* 1990; **162**: 788–792.
9. Barton JR, Sibai BM. Cerebral pathology in eclampsia. Hypertension and pregnancy. *Clinics in Perinatology* 1991; **18**: 891–910.
10. Belfort MA, Moise KJ. Effect of magnesium sulphate on brain blood flow in pre-eclampsia: a randomised placebo-controlled study. *American Journal of Obstetrics and Gynecology* 1992; **167**: 661–666.
11. Belfort MA, Uys P, Dommisse J, Davey DA. Hemodynamic changes in gestational proteinuric hypertension. The effects of rapid volume expansion and vasodilator therapy. *British Journal of Obstetrics and Gynaecology* 1989; **96**: 643–641.
12. Belizan JM, Villar J. The relationship between calcium intake and edema—proteinuria and hypertension gestosis. An hypothesis. *American Journal of Clinical Nutrition* 1980; **33**: 2202.
13. Benedetti TJ, Carlson RW. Studies of colloid osmotic pressure in pregnancy-induced hypertension. *American Journal of Obstetrics and Gynecology* 1979; **135**: 308–311.
14. Benedetti TJ, Kates R, Williams V. Hemodynamic observations in severe pre-eclampsia complicated by pulmonary oedema. *American Journal of Obstetrics and Gynecology* 1985; **152**: 330–334.
15. Boston JL, Beauchene RE, Guinkshank DP. Erythrocyte and plasma magnesium during teenage pregnancy: Relationship with blood pressure and pregnancy induced hypertension. *Obstetrics and Gynecology* 1989; 73: 169–174.
16. Brimacombe J. Acute pharyngolaryngeal oedema and pre-eclamptic toxemia. *Anesthesia and Intensive Care* 1992; **20**: 97–98.
17. Butters L, Kennedy S, Rubin PC. Atenolol in essential hypertension during pregnancy. *British Medical Journal* 1990; **301**: 587–589.
18. Carroli G, Duley L, Belizan JM, Villar J. Calcium supplements during pregnancy—a systematic review of randomised controlled trials. *British Journal of Obstetrics and Gynaecology* 1994; **101**: 753–758.
19. Catanzarite V, Quirk JG, Aisenbury G. How do perinatologists manage pre-eclampsia. *American Journal of Perinatology* 1991; **8**: 7–10.
20. Cheek TG, Samuels P. Pregnancy-induced hypertension. In: Datta S, ed. *Anesthetic and Obstetric Management of the High Risk Pregnancy.* St Louis: Mosby Year Book, 1991: 423–456.

21. Chelsey LC, Lindheuner MD. Renal hemodynamics and intravascular volume in normal and hypertensive pregnancy. In: Rubin PC, ed. *Handbook of Hypertension. Vol. 10. Hypertension in Pregnancy*. Amsterdam: Elsevier 1988: 38–65.
22. Chen FP, Chang SD, Chu KK. Expectant management in severe pre-eclampsia. Does magnesium sulphate prevent the development of eclampsia? *Acta Obstetrica et Gynecologica Scandinavica* 1995; 74: 181–185.
23. Chester EM, Agamanolis DP, Banker BQ, Victor M. Hypertensive encephalopathy: a clinicopathologic study of 20 cases. *Neurology* 1978; **28**: 928–939.
24. Chissell S, Botha JH, Moodley J, McFadyen L. Intravenous and intramuscular magnesium sulphate regimens in severe pre-eclampsia. *South African Medical Journal* 1994; **84**: 607–610.
25. Chua S, Redman CWG. Are prophylactic anti-convulsants required in severe pre-eclampsia? *Lancet* 1991; **337**: 250–251.
26. Clarke SL, Greenspoon JS, Adahl D, Phelan JP. Severe pre-eclampsia with persistent oliguria. Management of haemodynamic subjects. *American Journal of Obstetrics and Gynecology* 1986; **154**: 490–494.
27. Clark SL, Cotton DB. Clinical indications for pulmonary artery catherisation in the patient with severe pre-eclampsia. *American Journal of Obstetrics and Gynecology* 1988; **158**: 453–8.
28. CLASP (Collaborative Low-Dose Aspirin Study in Pregnancy). A randomised trial of low dose aspirin for the prevention and treatment of the pre-eclampsia among 9,364 pregnant women. *Lancet* 1994; **343**: 619–629.
29. Cooper DW, Bronneoke SP, Wilton AN. Genetics of pre-eclampsia. *Journal of Hypertension in Pregnancy* 1993; **12**: 1–23.
30. Cotton DB, Gonik B, Dorman KF. Cardiovascular alterations in severe pregnancy induced hypertension. Acute effects of intravenous magnesium sulphate. *American Journal of Obstetrics and Gynecology* 1984; **148**: 162–165.
31. Cotton DB, Janusz CA, Berman RF. Anticonvulsant effects of magnesium sulphate on hippocarpal seizures. Therapeutic implications in pre-eclampsia-eclampsia. *American Journal of Obstetrics and Gynecology* 1992; **116**: 1127–1131.
32. Cotton DB, Lee W, Huhta JC, Dorman KF. Hemodynamic profile in severe pregnancy induced hypertension. *American Journal of Obstetrics and Gynecology* 1988; **158**: 523–529.
33. Crowther C. Magnesium sulphate versus diazepam in the management of eclampsia. A randomised controlled trial. *British Journal of Obstetrics and Gynaecology* 1990; **97**: 110–117.
34. Crowther CA. Eclampsia at Harare Maternity Hospital. An epidemiological study. *South African Medical Journal* 1985; **68**: 927–929.
35. Cunningham FG, Fernandez CO, Hernandez C. Blindness associated with pre-eclampsia. *American Journal of Obstetrics and Gynecology* 1995; **172**: 1291–1298.
36. Dann WL, Hutchinson A, Cartwright DP. Maternal and neonatal responses to alfentanil administered before induction of anaesthesia for caesarean section. *British Journal of Anaesthesia* 1987; **59**: 1392–1396.
37. Davey DA. Hypertensive disorders of pregnancy. In: Whitefield, CR, ed. *Dewhurst's Textbook of Obstetrics and Gynaecology for Postgraduates*. Oxford: Science, 1995: 175–215.
38. Davey DA, Macgillivray I. The classification and definition of hypertensive disorders of pregnancy. *American Journal of Obstetrics and Gynaecology* 1988; **158**: 892–898.
39. de Jong CLD, Dekker GA, Sibai BM. The renin–angiotensin–aldesterone system in pre-eclampsia. Hypertension and pregnancy. *Clinics in Perinatology* 1991; **18**: 683–711.
40. Dekker GA, Kraayenbrink AA. Oxygen free radicals in pre-eclampsia. *American Journal of Obstetrics and Gynecology* 1991; **164**: (Suppl.) 273.
41. Dekker GS, Sibai BM. Early detection of pre-eclampsia. *American Journal of Obstetrics and Gynecology* 1991; **165**: 160–172.
42. Department of Health. Report on Confidential Enquiries into Maternal Deaths in the UK. 1988–90. London: DoH, 1994: 22–33.
43. Dommisse J. Phenytoin sodium and magnesium sulphate in the management of eclampsia. *British Journal of Obstetrics and Gynaecology* 1990; **97**: 104–109.
44. Donaldson JO. Does magnesium sulphate treat eclamptic convulsions? *Clinical Neuropharmacology* 1986; **9**: 37–45.
45. Douglas KA, Redman CWG. Eclampsia in the United Kingdom. *British Medical Journal* 1994; **309**: 1395–1400.
46. Easterling TR, Watts DH, Schmucker BC, Benedetti TJ. Measurement of cardiac output during pregnancy; validation of Doppler technique and clinical observation in pre-eclampsia. *Obstetrics and Gynaecology* 1987; **69**: 845–850.
47. Editorial. Bed rest and non-proteinuric hypertension in pregnancy. *Lancet* 1992; **339**: 1023–1024.
48. Egley CC, Guthlip JA, Bowes WA. Severe hypoglycemia associated with HELLP syndrome. *American Journal of Obstetrics and Gynecology* 1985; **152**: 576–577.
49. Ellis SC, Wheeler AS, James III FM, Rose JC, Meis PJ, Shihabi Z, Greiss FC, Urban RB. Fetal and maternal effects of sodium nitroprusside used to counteract hypertension in gravid ewes. *American Journal of Obstetrics and Gynecology* 1982; **143**: 766–770.
50. Freidman EA, Neff RK. *Pregnancy hypertension. A systemic evaluation of clinical diagnostic criteria*. Littleton, MA: PSG Publishing, 1977: 239.
51. Freidman SA, Taylor RN, Roberts JM. Pathophysiology of pre-eclampsia: hypertension and pregnancy. *Clinics in Perinatology* 1991; **18**: 661–682.
52. Gaitz JP, Bamford CR. Unusual computed tomographic scan in eclampsia. *Archives of Neurology* 1982; **39**: 66.
53. Greer IA, Dawes J, Johnstone TA, Calder AA. Neutrophil activation is confined to the maternal circulation in pregnancy induced hypertension. *Obstetrics and Gynaecology* 1991; **78**: 28–32.
54. Groenedijk R, Trimbos JBMJ, Wallenburg HCS. Hemodynamic measurements in pre-eclampsia. Preliminary observations. *American Journal of Obstetrics and Gynaecology* 1984; **150**: 232–236.
55. Hanssens M, Kierse MJNC, Vankelocom F, Van Assche FA. Fetal and neonatal effects of treatment with angiotensin converting enzymes inhibitors in pregnancy. *Obstetrics and Gynecology* 1991; **78**: 128–135.
56. Heavey DJ, Barrow SE, Hickling NE, Ritter JM. Aspirin causes short-lived inhibition of bradykinin-stimulated prostacyclin production in man. *Nature* 1985; **318**: 186–188.
57. Hibbard BM, Rosen M. The management of severe pre-eclampsia and eclampsia. *British Journal of Anaesthesia* 1977; **49**: 3–9.
58. Hood DD, Boese PA. Epidural and spinal anesthesia for caesarean section in severely pre-eclamptic patients (abstract). *Regional Anesthesia* 1992; **17**: 35.
59. Hutton JD, James DK, Stirrat DKA, Redman CW. Management of severe pre-eclampsia and eclampsia by UK consultants. *British Journal of Obstetrics and Gynaecology* 1992; **99**: 554–556.
60. Imperiale TF, Petrulis AS. A meta-analysis of low dose aspirin for the prevention of pregnancy induced hypertensive disease. *Journal of the American Medical Association* 1991; **266**: 260–265.
61. Ismail AA, Medhat I, Tawfic TA, Kholeif A. Evaluation of calcium antagonist (Nifedipine) in the treatment of pre-eclampsia. *International Journal of Gynecology and Obstetrics* 1993; **40**: 30–43.
62. Italian Study of Aspirin in Pregnancy. Low dose aspirin in prevention and treatment of intrauterine growth retardation and pregnancy-induced hypertension. *Lancet* 1993; **341**: 396–400.
63. James MFM, Beer RE, Esser JD. Intravenous magnesium sulphate inhibits catecholamine release associated with tracheal intubation. *Anesthesia and Analgesia* 1989; **68**: 772–776.
64. Jouppila P, Jouppila R, Hollmen A, Koivula A. Lumbar epidural analgesia to improve intervillous blood flow during labour in severe pre-eclampsia. *Obstetrics and Gynecology* 1982; **59**: 158–161.
65. Jouppila P, Kuikka J, Jouppila R, Hollmen A. Effect of induction of general anaesthesia for cesarean section on intervillous blood flow. *Acta Obstetrica et Gynecologica Scandinavica* 1979; **58**: 249–253.
66. Joyce III TH, Debnath KS, Baker EA. Pre-eclampsia—relationship of CVP and epidural analgesia (abstract). *Anesthesiology* 1979; **51**: 5297.

67. Kambain JR, Handle RE, Brown WU, Smith BE. Effect of normal and pre-eclamptic pregnancies on the oxyhemoglobin dissociation. *Anesthesiology* 1986; **65**: 426–427.
68. Kelton JG, Hunter DJS, Neame PB. A platelet function defect in pre-eclampsia. *Obstetrics and Gynecology* 1985; **65**: 107–109.
69. Kirby JC, Jaindl JJ. Cerebral CT findings in toxaemia of pregnancy. *Radiology* 1984; **151**: 114.
70. Kirshon B, Lee W, Mauer MB, Cotton DB. Effects of low dose dopamine therapy in the oliguric patient with pre-eclampsia. *American Journal of Obstetrics and Gynecology* 1988; **159**: 604–7.
71. Kirshon B, Moise KJ, Cotton DB, Longmire S, Jones M, Tessem J, Joyce III TA. Role of volume expansion in severe pre-eclampsia. *Surgery Gynecology and Obstetrics* 1988; **167**: 367–371.
72. Lawes EG, Downing JW, Duncan PW, Bland B, Lavies N, Gane GAC. Fentanyl-droperidol supplementation of rapid sequence induction in the presence of severe pregnancy-induced and pregnancy aggravated hypertension. *British Journal of Anaesthesia* 1987; **59**: 1381–1391.
73. Lee W, Gonik B, Cotton DB. Urinary diagnostic indices in pre-eclampsia-associated oliguria. Correlation with invasive hemodynamic monitoring. *American Journal of Obstetrics and Gynecology* 1987; **156**: 100–103.
74. Lever JCW. Cases of puerperal convulsions; with remarks. *Guys Hospital Reports* 1843; **1**: 495–517.
75. Letsky EA. Haemostasis and epidural anaesthesia. *International Journal of Obstetric Anaesthesia* 1991; **1**: 51–54.
76. Levin AC, Doering PL, Hutton RC. Use of nifedipine in the hypertensive diseases of pregnancy. *Annals of Pharmacotherapy* 1994; **28**: 1371–1378.
77. Lindow SW, Davies N, Davey DA, Smith JA. The effect of sublingual nifedipine on uteroplacental blood flow in hypertensive pregnancy. *British Journal of Obstetrics and Gynaecology* 1988; **95**: 1276–1281.
78. Loevinger EH, Viujic I, Lee WM, Anderson MC. Hepatic rupture associated with pregnancy. Treatment with transcatheter embolotherapy. *Obstetrics and Gynecology* 1985; **65**: 281–285.
79. Longmire S, Leduc L, Jones MM, Hawkins JL, Joyce TH, Cotton DB. The hemodynamic effects of intubation during nitroglycerine infusion in severe pre-eclampsia. *American Journal of Obstetrics and Gynecology* 1991; **164**: 551–556.
80. Lopez-Llera M, Linares GR, Horta JLH. Maternal mortality rates in eclampsia. *American Journal of Obstetrics and Gynecology* 1976; **124**: 149–155.
81. Lucas MJ, Leveno KJ, Cunningham FG. A comparison of magnesium sulphate with phenytoin for the prevention of eclampsia. *New England Journal of Medicine* 1995; **333**: 201–205.
82. Lyall F, Greer JA. Pre-eclampsia: A multifaceted vascular disorder of pregnancy. *Journal of Hypertension* 1994; **12**: 1339–1345.
83. Mabie WC, Ratts TE, Sibai BM. The central hemodynamics of severe pre-eclampsia. *American Journal of Obstetrics and Gynecology* 1989; **161**: 1443–1448.
84. MacGillivray I. Some observations on the incidence of pre-eclampsia. *Journal of Obstetrics and Gynaecology* 1958; **65**: 536–539.
85. MacGillivray I, Rose GA, Rowe B. Blood pressure survey in pregnancy. *Clinical Science* 1969; **37**: 395–407.
86. Managing high blood pressure. *Drugs and Therapeutics Bulletin* 1993; **31** (14): 53–56.
87. Masaki DI, Greenspoon JS, Ouzouman JG. Measurement of cardiac output in pregnancy by thoracic electrical bi-impedance and thermodilution. *American Journal of Obstetrics and Gynecology* 1989; **161**: 680–684.
88. Maxwell MH, Waks AU, Schroth PC, Karam M, Dornfeld LP. Error in blood pressure measurement due to incorrect cuff size in obese patients. *Lancet* 1982; **ii**: 33–36.
89. Milliez J, Dahoun A, Boudra M. Computed tomography of the brain in eclampsia. *Obstetrics and Gynecology* 1990; **75**: 975–980.
90. Naden RP, Redman CWG. Antihypertensive drugs in pregnancy. *Clinics in Perinatology* 1985; **12** (3): 521–538.
91. Naeye CL, Freidman EA. Causes of perinatal death associated with gestational hypertension and proteinuria. *American Journal of Obstetrics and Gynecology* 1979; **133**: 8–10.
92. National High Blood Pressure Education Programme Working Group, report on high blood pressure in pregnancy. *American Journal of Obstetrics and Gynecology* 1990; **163**: 1689–1712.
93. Newsome LR, Bramwell RS, Curling PE. Severe pre-eclampsia: hemodynamic effects of lumbar epidural anesthesia. *Anesthesia and Analgesia* 1986; **65**: 31–36.
94. O'Dowd MJ, Philipp EE. The history of obstetrics and gynecology. New York: Parthenon Publishing Group, 1994: 93–96.
95. Oian P, Maltan JM, Noddeland H, Fadnes HO. Transcapillary fluid balance in pre-eclampsia. *British Journal of Obstetrics and Gynaecology* 1986; **93**: 235–239.
96. Potgieter PH, Hammond JMJ. Cuff test for safe extubation following laryngeal oedema. *Critical Care Medicine* 1988; **16**: 818.
97. Pritchard JA, Cunningham FG, Mason RA. Coagulation changes in eclampsia. Their frequency and pathogenesis. *American Journal of Obstetrics and Gynecology* 1976; **124**: 855–864.
98. Pritchard JA, Weisman R, Ratnoff OD, Vasburg GJ. Intravascular hemolysis, thrombocytopenia and other hematologic abnormalities associated with severe toxaemia of pregnancy. *New England Journal of Medicine* 1954; **250**: 89–98.
99. Rackow EC, Fein AI, Lippo J. Colloid osmotic pressure as a prognostic indicator of pulmonary oedema and mortality in the critically ill. *Chest* 1977; **72**: 709.
100. Ramanathan J. Pathophysiology and anesthetic implications in pre-eclampsia. *Clinical Obstetrics and Gynecology* 1992; **35**: 414–425.
101. Ramanathan J, Bottorff M, Jeter JN, Khalil M, Sibai BM. The pharmacokinetics and maternal and neonatal effects of epidural lidocaine in pre-eclampsia. *Anesthesia and Analgesia* 1986; **65**: 120–126.
102. Ramanathan J, Coleman P, Sibai BM. Anaesthetic modification of hemodynamic and neuroendocrine responses to cesarean delivery in women with severe pre-eclampsia. *Anesthesia and Analgesia* 1991; **73**: 772–779.
103. Ramanathan J, Sibai BM, Mabie WC, Chauhan D, Ruiz AG. The use of labetalol for attenuation of the hypertensive response to endotracheal intubation in pre-eclampsia. *American Journal of Obstetrics and Gynecololgy* 1988; **159**: 650–654.
104. Ramanathan J, Sibai BM, Vu T, Chauhan D. Correlation between bleeding times and platelet counts in women with pre-eclampsia undergoing cesarean section. *Anesthesiology* 1989; **71**: 188–191.
105. Redman CWG, Denson KWE, Beilin LJ, Bolton FG, Stirrat GM. Factor VIII consumption in pre-eclampsia. *Lancet* 1977; **ii**: 1249–1252.
106. Redman CWG, Jeffries M. Revised definition of pre-eclampsia. *Lancet* 1988; **i**: 809–812.
107. Redman CWG, Roberts JM. Management of pre-eclampsia. *Lancet* 1993; **341**: 1451–1454.
108. Roberts JM, Redman CWG. Pre-eclampsia: more than pregnancy-induced hypertension. *Lancet* 1993; **341**: 1447–1450.
109. Robillard P-Y, Hulsey TC, Perianin J, Janky E, Miri EH, Papiernik E. Association of pregnancy induced hypertension with duration of sexual co-habitation before conception. *Lancet* 1994; **344**: 973–975.
110. Robson S, Howell P. Report of a Royal College of Obstetrics and Gynaecology meeting 1994 on hypertension in pregnancy. *British Journal of Obstetrics and Gynaecology* 1994; **101**: 639–644.
111. Rocke DA, Scoones GP. Rapidly progressive laryngeal oedema associated with pregnancy aggravated hypertension. *Anaesthesia* 1992; **47**: 141–143.
112. Rogers GM, Taylor RN, Roberts JM. Pre-eclampsia associated with a serum factor cytotoxic to human endothelial cells. *American Journal of Obstetrics and Gynecology* 1988; **159**: 908–914.
113. Rout CC, Rocke DA. Effects of alfentanil and fentanyl on induction of anaesthesia inpatients with severe pregnancy-induced hypertension. *British Journal of Anaesthesia* 1990; **65**: 468–474.
114. Schnindler M, Gatt S, Isert P, Morgan D, Cheung A. Thrombocytopenia and platelet functional defects in pre-

eclampsia. Implications for regional anaesthesia. *Anaesthesia and Intensive Care* 1990; **18**: 169–174.

115. Schwaighofer BW, Hesselink JR, Healy ME. MR demonstration of reversible brain abnormalities in eclampsia. *Journal of Computer Assisted Tomography* 1989; **13**: 310–312.
116. Sheehan HL, Lynch JB. Cerebral lesions. In: *Pathology of Toxaemia of Pregnancy*. Baltimore: Williams and Wilkins, 1973: 524.
117. Sibai BM. Magnesium sulphate is the ideal anticonvulsant in pre-eclampsia/eclampsia. *American Journal of Obstetrics and Gynecology* 1990; **162**: 1141–1145.
118. Sibai BM. The HELLP syndrome (Hemolysis, elevated liver enzymes and low platelets): much ado about nothing. *American Journal of Obstetrics and Gynecology* 1990; **162**: 311–316.
119. Sibai BM. Eclampsia—maternal and perinatal outcome in 254 consecutive cases. *American Journal of Obstetrics and Gynaecology* 1990; **163**: 1049–1055.
120. Sibai BM, Anderson GD, Spinnato JA, Shaver DC. Plasma volume findings in patients with mild pregnancy induced hypertension. *American Journal of Obstetrics and Gynecology* 1983; **147**: 16–19.
121. Sibai BM, Caritis SN, Thom E, Klebanoff M, Mcnells D, Rocco L, Paul RH, Romero R, Wilter F, Rosen F, Depp R. Prevention of pre-eclampsia with low dose aspirin in healthy, nulliparous pregnant women. *New England Journal of Medicine* 1993; **329**: 1213–1218.
122. Sibai BM, Mabie WC. Hemodynamics of pre-eclampsia. Pregnancy and hypertension. *Clinics in Perinatology* 1991; **18**: 727–747.
123. Sibai BM, Mabie BC, Harvey CT, Gonzalez AR. Pulmonary oedema in severe pre-eclampsia-eclampsia. Analysis of thirty-seven consecutive cases. *American Journal of Obstetrics and Gynecology* 1987; **156**: 1174–1179.
124. Sibai BM, McCubbin JH, Andersson GD, Lipshitz JA, Dilts PV. Eclampsia I. Observations from 67 recent cases. *Obstetrics and Gynecology* 1981; **58**: 609–613.
125. Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Freidman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes and low platelets (HELLP syndrome). *American Journal of Obstetrics and Gynecology* 1993; **169**: 1000–1006.
126. Sibai BM, Spinnato JA, Watson DL, Hill GA, Anderson GD. Pregnancy outcome in 303 cases with severe pre-eclampsia. *Obstetrics and Gynecology* 1984; **64**: 319–325.
127. Sibai BM, Spinnato JA, Watson DL, Lewis JA, Anderson GD. Effects of magnesium sulphate on electroencephalographic findings in pre-eclampsia-eclampsia. *Obstetrics and Gynecology* 1984; **64**: 261–266.
128. Sibai BM, Taslimi MM, El-Nazer A, Amon E, Mabie BC, Ryan GM. Maternal-perinatal outcome associated with the syndrome of hemolysis, elevated liver enzymes and low platelets in severe pre-eclampsia-eclampsia. *American Journal of Obstetrics and Gynecology* 1986; **155**: 501–509.
129. Sibai BM, Villar MA, Mabie BC. Acute renal failure in hypertensive disorders of pregnancy. Pregnancy outcome and remote prognosis in thirty one consecutive cases. *American Journal of Obstetrics and Gynecology* 1990; **162**: 777–783.
130. Sinatra RJ, Philip BL, Naulty JS, Ostheimer GW. Prolonged neuromuscular blockade with vecuronium in a patient treated with magnesium sulphate. *Anesthesia and Analgesia* 1985; **64**: 1220–1222.
131. Sosis M, Leighton B. In defense of trimetaphan for use in pre-eclampsia. *Anesthesiology* 1986; **64**: 657–658.
132. Spatling L, Spatling G. Magnesium supplementation in pregnancy: A double blind study. *British Journal of Obstetrics and Gynaecology* 1988; **95**: 120.
133. Spinillo A, Capuzzo E, Colousa L, Solerte L, Nicola S, Guaschino S. Factors associated with abruptio placentae in preterm deliveries. *Acta Obstetrica et Gynecologica Scandinavica* 1994; **73**: 307–312.
134. Steel SA, Pearce JM, McParland P, Chamberlain GVP. Early doppler ultrasound screening in prediction of hypertensive disorders of pregnancy. *Lancet* 1990; **335**: 1548–1551.
135. Stempel JE, O'Grady JP, Morton MJ, Johnson KA. Use of sodium nitroprusside in complication of gestational hypertension. *Obstetrics and Gynecology* 1982; **60**: 533–538.
136. Taylor RN, Crombleholme WR, Freidman SA, Jones LA, Casal DC, Roberts JM. High plasma cellular fibronectin levels correlate with biochemical and clinical features of pre-eclampsia but cannot be attributed to hypertension alone. *American Journal of Obstetrics and Gynaecology* 1991; **165**: 895–901.
137. The Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet* 1995; **345**: 1455–1463.
138. Thiagarajah S, Bourgeois FJ, Harbet GM, Caudle MR. Thrombocytopenia in pre-eclampsia: Associated abnormalities and management principles. *American Journal of Obstetrics and Gynecology* 1984; **150**: 1–7.
139. Thornton JC, Onwode JL. Pre-eclampsia: discordance among identical twins. *British Medical Journal* 1991; **303**: 1241–1242.
140. Veille JC, Hosenpud JD, Morton JM. Cardiac size and function in pregnancy induced hypertension. *American Journal of Obstetrics and Gynecology* 1984; **150**: 443.
141. Villar J, Repke JT. Calcium supplements during pregnancy may reduce preterm delivery in high risk populations. *American Journal of Obstetrics and Gynecology* 1990; **163**: 1124–1131.
142. Waisman GP, Mayorga LM, Camera MI, Vignolo CA, Martinotti A. Magnesium plus nifedipine: Potentiation of hypotensive effect in pre-eclampsia. *American Journal of Obstetrics and Gynecology* 1988; **159**: 308–309.
143. Weinstein L. Syndrome of hemolysis, elevated liver enzymes, low platelet count: a severe consequence of hypertension on pregnancy. *American Journal of Obstetrics and Gynecology* 1982; **142**: 159–167.
144. Woods DL, Molar AF. Side effects of labetalol in new born infants. *British Journal of Obstetrics and Gynaecology* 1983; **90**: 876.
145. Writer D. *Hypertensive Disorders in Obstetric Anaesthesia, Principles and Practices*. Chestnut, DH: Mosby, 1994; 847.
146. Zinaman M, Rubin J, Lindheimer MD. Serial plasma oncotic pressure levels and echoencephalography during and after delivery in severe pre-eclampsia. *Lancet* 1985; **1**: 1245–1247.

British Journal of Anaesthesia 1996; **76**: 149–150

SHORT COMMUNICATIONS

Extradural and subarachnoid catheterization using the Seldinger technique

E. M. DELHAAS

Summary

The Seldinger technique was developed using a plastic introducer through which introduction and manipulations of a silicone spinal catheter, an extradural stimulation lead or a small diameter fibreoptic scope are possible without the risk of damage to the vulnerable devices. It is not intended as a replacement of the standard technique of introducing a spinal catheter through a Tuohy needle in general anaesthetic practice. Silicone spinal catheters and stimulation leads are used for long-term therapy in intractable chronic pain and spasticity. A fibreoptic scope is used for endoscopic examination of the subarachnoid or extradural space. Using a standard Tuohy needle the soft silicone extradural lead can be damaged easily by manipulations during insertion. For this reason the manufacturer modified the Tuohy needle for extradural silicone lead introduction. The disadvantages of this modified Tuohy needle are: first, difficulty in localization of the extradural space, second, the needle is unsuitable for a subarachnoid catheter or introduction of a fibreoptic scope. The Seldinger technique was performed 25 times in 18 patients, introducing a spinal silicone catheter ($n = 14$), an extradural silicone stimulation lead ($n = 2$) or a small diameter fibreoptic endoscope ($n = 9$). Paraesthesiae caused by neural irritation occurred in awake patients. This did not differ from the technique using a Tuohy needle only. Neural damage or trauma did not occur with the Seldinger technique. The incidence of post-spinal headache was the same for both techniques. No further complications were noted. (*Br. J. Anaesth.* 1996; **76**: 149–150)

Key words
Anaesthetic techniques, subarachnoid. Equipment, catheters extradural. Equipment, catheters subarachnoid.

Implanted drug delivery systems are used for managing intractable chronic pain and spasticity with continuous subarachnoid drug infusion [1, 2]. Long-term experience shows a rather high spinal catheter complication rate [2]. One of the problems is damage to the silicone spinal catheter during insertion. This could be caused by the sharp edges of the Tuohy needle and it is possible that this may completely cut the catheter resulting in a catheter segment remaining in the subarachnoid space.

Advancing a lead for spinal cord stimulation or a small diameter fibreoptic endoscope [3] through a Tuohy needle is potentially hazardous. For this reason, the manufacturer has modified the Tuohy needle for extradural silicone lead introduction. The disadvantages of this modified Tuohy needle for extradural lead introduction are: first, difficulty in localization of the extradural space and second, the needle is still unsuitable for use with a subarachnoid silicone catheter or fibreoptic scope.

When using a paramedian approach for subarachnoid catheterization, less damage to the catheter can be expected than with the classic median approach. However, the risk of damage to the catheter cannot be completely avoided.

This study was designed to determine the usefulness of the Seldinger technique [4] which allows insertion of a catheter, lead or fibreoptic scope through a plastic sheath into the subarachnoid space.

Methods and results

Local Ethics Committee approval and informed patient consent were obtained. The efficacy of the Seldinger technique for subarachnoid and extradural insertion was studied 25 times in 18 patients (14 with a subarachnoid catheter, two with an extradural stimulation lead and nine with a small diameter fibreoptic endoscope).

With the patient in the lateral position, using the median or paramedian approach, a lumbar puncture with a Tuohy needle (Perican 16 G, B. Braun Melsungen AG, Melsungen, Germany) was performed. A commercially available vascular introduction kit (Check-Flo II Introduction Set 5 Fr, William Cook Europe A/S, Bjaeverskov, Denmark) was used for the Seldinger technique. Under fluoroscopic control a guide wire was advanced through the needle 5–10 cm into the subarachnoid space. By sliding it over the guide wire, the Tuohy needle was removed. The plastic catheter sheath with the dilator was then advanced over the guide wire. Successively the guide wire and dilator were removed. Through the sheath the spinal catheter (Implantable Spinal Catheter 8703 and 8706, Medtronic Inc., Minneapolis, USA), lead (Pisces Quad 3487A, Medtronic Inc., Minneapolis, USA) or a 1.4-mm

---

E. M. DELHAAS, MD, Department of Anaesthesia, Sophia Hospital, Dr van Heesweg 2, PO Box 10400, 8000 GK Zwolle, The Netherlands. Accepted for publication: August 2, 1995.

fibreoptic endoscope (Olympus Europe, Hamburg, Germany) could then be introduced easily.

In four cases post-spinal headaches were observed, which were treated successfully with a homologous blood patch. No other complications were observed.

Comment

This study has indicated that the Seldinger technique is an effective method of inserting an extradural catheter, lead or fibrescope into the subarachnoid space. When a Tuohy needle is used for subarachnoid cannulation, the sharp needle edges are potentially damaging. In particular, retrograde movements through the needle have to be avoided. When these movements are necessary it is strongly advised to remove the Tuohy needle together with the catheter and to repeat the lumbar puncture. This can be difficult in severely spastic patients. Furthermore, re-insertion of the rather large diameter Tuohy needle increases the risk of CSF leakage. The most important advantage of the Seldinger technique is that frequent manipulations through the plastic introducer in fibreoptic spinaloscopy and in difficult subarachnoid catheter and extradural lead insertion can now be performed without adverse effects to the apparatus.

With the modified Tuohy needle (Pisces Quad 3487A, Medtronic Inc., Minneapolis, USA) introduction of a stimulation lead in the extradural space is hampered. By using the Seldinger technique, a standard Tuohy needle is used and the extradural space can be identified easily with the loss of resistance method.

The use of the plastic sheath in the Seldinger technique is very important. It protects the fibreoptic scope during multidirectional manipulations. Introduction of a plastic sheath with its silicone membrane into the spinal space gives far superior control on CSF fluid loss. A frustrating complication of chronic spinal drug delivery systems is disconnection of the two spinal catheter parts [2]. A single piece spinal catheter with a plastic introducer sheath which may be split and removed is in the process of development.

Spinal puncture with a Tuohy needle has a high incidence of post-spinal headache [2]. The incidence of spinal headache in our patients treated with the Seldinger technique was similar to that using the classic Touhy needle spinal puncture technique. The use of a guide wire in the Seldinger technique does not differ from the original technique of introducing a spinal silicone catheter and seems therefore to be an acceptable technique.

The technique is thought to be atraumatic and hopefully may lead to a reduction in catheter morbidity in long-term use. There were no short- or long-term neurological sequelae in the patients reported here. Further studies in this area would be valuable.

Acknowledgements

We thank Olympus Optical Europe, Hamburg, Germany, for the supply of the small diameter fibreoptic endoscope and Medtronic Inc., Kerkrade, The Netherlands for the implantable spinal catheter 8706.

References

1. Penn RD, Savoy SM, Corcos D, Latash M, Gottlieb G, Parke M, Kroin JS. Intrathecal baclofen for severe spinal spasticity. *New England Journal of Medicine* 1989; **320**: 1517–1521.
2. Ochs G, Delhaas EM. Long-term experience with intrathecal use of baclofen in severe spasticity. In: Lakke JPWF, Delhaas EM, Rutgers AWF, eds. *New Trends in Clinical Neurology: Parenteral Drug Therapy in Spasticity and Parkinson's Disease.* Lancs: Parthenon, 1992; 87–102.
3. Shimoji K, Fujioka H, Onodera M, Hokari T, Fukuda S, Fujiwara N, Hatori T. Observation of spinal canal and cisternae with the newly developed small-diameter, flexible fibrescopes. *Anesthesiology* 1991; **75**: 341–344.
4. Seldinger SI. Catheter replacement of the needle in percutaneous arteriography. *Acta Radiologica* 1953; **39**: 368–376.

British Journal of Anaesthesia 1996; **76**: 151–153

Regional anaesthesia for outpatient nasal surgery

S. MOLLIEX, M. NAVEZ, D. BAYLOT, J. M. PRADES, Z. ELKHOURY AND C. AUBOYER

Summary

Regional anaesthesia is not used widely for outpatient nasal surgery. The aim of this study was to determine the role of nasociliary and infraorbital nerve block in 24 patients undergoing nasal surgery comprising: cosmetic or reconstructive surgery of the nose and surrounding soft tissue, polypal removal, turbinectomy, reduction of fractured nasal bones, small tumour resection or emergency surgery on isolated facial lacerations. Mild sedation with midazolam 0.03 mg kg^{-1} was used before anaesthesia. Nasociliary and infraorbital blocks were technically easy to perform, safe and provided good intraoperative conditions. Only minor complications were observed, including local bruising in eight patients and transient diplopia in one patient. No patient received general anaesthesia, but infiltration of local anaesthetic was necessary in four patients because of incomplete anaesthesia in the surgical area. Operative conditions were judged as good or excellent by surgeons in 20 of 24 patients. Twenty of 24 patients were very satisfied or satisfied with anaesthesia. Duration of surgery exceeding 60 min and excessive bleeding in the nasopharynx were the main limiting factors for the use of facial regional anaesthesia. (*Br. J. Anaesth.* 1996; **76**: 151–153)

Key words

Anaesthetic techniques, regional. Anaesthesia, day-case. Surgery, facial. Surgery, plastic.

Regional anaesthesia of the face is used commonly for diagnosis or neurolytic blocks for chronic pain syndromes. However, these techniques have limited use as safer general anaesthesia has developed because of the discomfort and stress produced by facial surgery. Facial surgery is very frequently performed on an outpatient basis, especially for minor procedures involving the soft tissues of the nose, cheek, lower eyelid and upper lip. Regional anaesthesia may offer several advantages for the ambulatory patient, including: avoidance of the common side effects of general anaesthesia and tracheal intubation; decrease in patient recovery time; and residual analgesia in the early postoperative period [1]. The purpose of this study was to evaluate if outpatient nasal surgery performed under regional anaesthesia was safe and not accompanied by severe discomfort.

Methods and results

After obtaining informed consent, we studied 24 patients, mean age 36 yr (range 19–62 yr). Nineteen patients were scheduled for different nasal surgical procedures including: cosmetic or reconstructive surgery of the nose and surrounding soft tissue (12), polypal removal (1), turbinectomy (2), reduction of fractured nasal bones (2) and resection of small tumours (2). Five patients with a "full stomach" were managed as emergencies for isolated nasal or upper lip lacerations, or both, after facial trauma. Regional anaesthesia was performed on each side by block of the infraorbital nerve and nasal branches of the nasociliary nerve, with patient supine.

The nasociliary nerve is a branch of the ophthalmic nerve giving off several important groups of branches while in the orbital cavity. The ethmoidal branches supply the mucous membrane of the sphenoidal, ethmoidal and frontal sinuses. The nasal branches supply the mucous membrane of the anterior part of the septum, the lateral wall of the nasal cavity, and the skin of the ala and apex of the nose by the internal and external branches, respectively [2]. To block the nasociliary nerve or its branches, a 3-cm, 25-gauge needle was inserted 1 cm above the inner canthus and directed posterolaterally, keeping contact with bone. At a depth of 1.5 cm the needle should be at the anterior ethmoidal foramen, and 2 ml of anaesthetic solution was then injected. The needle was then advanced slowly 1 cm further to reach the posterior ethmoidal foramen where 1.5 ml of solution was injected to block the posterior ethmoidal nerve that supplies the posterior sinuses. The two injections were also likely to block another branch of the nasociliary nerve, the infratrochlear nerve which supplies the root of the nose [3].

The infraorbital nerve is a terminal cutaneous branch of the maxillary nerve emerging through the infraorbital foramen. It divides into three groups of branches supplying the skin of the nose and the septum mobile nasi, the upper lip and its mucosa, and the lower eyelid and its conjunctiva [2]. To block the infraorbital nerve, an oral approach was performed as follows: the infraorbital foramen was

---

S. MOLLIEX, MD, M. NAVEZ, MD, D. BAYLOT, MD, Z. ELKHOURY, MD, C. AUBOYER, MD (Département d'Anesthésie et de Réanimation Chirurgicale); J. M. PRADES, MD (Service de Chirurgie Cervico-Faciale et Plastique, Pr Martin); CHRU de Saint-Etienne, Hôpital Bellevue, Bd Pasteur, 42055 St-Etienne Cedex 2, France. Accepted for publication: August 9, 1995.

Correspondence to S.M.

palpated approximately 2.5 cm from the midline of the face, on an imaginary straight line passing through the supraorbital notch, the pupil of the eye, the infraorbital foramen and the second bicuspid tooth. Depression of the foramen was fixed with a finger while a 3-cm, 25-gauge needle was inserted in the mucobuccal fold along the axis of the bicuspid tooth. The needle tip was advanced, being guided by the finger over the foramen. Anaesthetic solution (3 ml) was injected in the vicinity of the foramen without entering the canal [4].

Blocks were carried out with a mixture of equal volumes of 0.25 % bupivacaine and 1 % lignocaine with adrenaline 1:400000. The nasociliary blocks were produced without adrenaline to eliminate any risk of retinal artery spasm. In addition, for surgical procedures involving the mucous membrane of the superior and middle turbinates and the posterior part of the septum, topical anaesthesia of the nasal branches of the pterygopalatine nerves was performed on each side. These branches lie on the lateral wall of the nasal passage, just posterior to the middle turbinate. A small piece of gauze soaked in a mixture of 5 % lignocaine and 0.25 % phenylephrine was introduced along the middle turbinate and placed at the end of the nasal passage for at least 10 min [3]. This combination of vasoconstrictor and anaesthetic agent reduced bleeding during surgery. The nasociliary and infraorbital nerve blocks were considered adequate in the first instance, if the apex and the skin on the side of the nose were anaesthetized, respectively. I.v. sedation was administered before anaesthesia with midazolam 0.03 mg kg^{-1}.

The following variables were assessed: time to full sensory loss in the anaesthetized area, tolerance of the surgical procedure estimated by the surgeon on a four-point scale (excellent, good, fair or poor), time to recover light touch and patient satisfaction after surgery on a four-point scale (very satisfied, satisfied, little satisfied or dissatisfied).

Sixty-seven blocks were produced, including 42 nasociliary and 25 infraorbital blocks. They were associated with topical anaesthesia of the pterygopalatine nerves in only seven patients. Depending on the surgical procedure, the number of blocks performed on each patient was 1, 2, 3 and 4 for 2, 11, 1 and 10 patients, respectively. The blocks were frequently bilateral, particularly for surgical procedures involving the nasal cavity. Mean time to full sensory loss was 11 (range 5–15) min, mean duration of surgery was 45 min (range 15–90 min), and mean duration of block before recovery of light touch sensory was 1 h 31 min (range 30 min–2 h 30 min). However, the latter result was affected by the use of lignocaine alone for the two shortest surgical procedures (15 min). No patient received general anaesthesia, but infiltration of local anaesthetics was necessary in four patients because of incomplete anaesthesia in the surgical area. Additional administration of midazolam was necessary during surgery in 11 patients without exceeding a dose of 0.05 mg kg^{-1}. The minor side effects of nasociliary blocks were: a little bruise and swelling of the upper lid in eight patients and diplopia disappearing as the block dissipated in one other patient. In our study, an intraoral approach was performed to block the infraorbital nerve. By using this approach and a 3-cm, 25-gauge needle, no haematoma was noticed. Tolerance of the surgical procedure was considered fair (2) or poor (2) in four patients compared with good (16) or excellent (4) in 20 patients. Twenty-two patients were very satisfied (10) or satisfied (12), but two patients were dissatisfied because of the feeling of suffocation from draping the face (one) and swallowing of blood (one).

Comment

The results of the present study demonstrated that regional anaesthesia is suitable for outpatient nasal surgery.

Nasociliary and infraorbital blocks are technically easy to perform, safe and provide good intraoperative conditions. These blocks also produce good anaesthesia. Indeed, nasociliary and infraorbital nerves blocks are considered adequate in the first place if the apex and side of the nose are anaesthetized, respectively. Because adrenaline is not used for the nasociliary block to prevent any risk of retinal artery spasm, this block wears off first. Thus, the mean duration of block represents the mean duration of anaesthesia in the area supplied by the nasociliary nerves. This could explain the short duration of block in our study. Consequently, we suggest that the infraorbital nerve is blocked before nasociliary block, even if the duration of anaesthesia is not increased significantly because of the short time taken to block the infraorbital nerve. The failure rate was 16 % (4/24), which is low with regard to the total number of blocks carried out (67). This rate included only partial failure allowing surgery to proceed with single local anaesthetic infiltration. In addition, in the case of unilateral surgery, a smaller number of injections is required to perform anaesthesia, and this also decreases the risk of failure.

All of the failures involved the nasal cavity. However, it is extremely difficult to be certain each time which are the appropriate blocks because the areas supplied by the nasociliary and pterygopalatine nerves overlap. The lack of pterygopalatine nerve block may be responsible for some failures reported in our study. No major complication was observed and swelling of eyelid, the more common side effect of nasociliary block, may be prevented by local pressure during anaesthetic injection. The time to prepare and perform the blocks, and the onset time are appropriate for the outpatient setting. Light sedation with midazolam allows anaesthetic and surgical procedures to be performed without severe discomfort and stress, as assessed by patient satisfaction.

The amnesic effect of midazolam may make it difficult to assess adequately "patient satisfaction". However, midazolam was used in small doses (0.03 mg kg^{-1}) to relieve anxiety just before the blocks were carried out and a dose of 0.05 mg kg^{-1} was not exceeded. We do not believe that in these doses the amnesic effects of midazolam dramatically modified patient assessment of satisfaction. However, duration of surgery exceeding 60 min and excessive bleeding in the nasopharynx are felt as unpleasant and represent the main limiting factors the use of regional anaesthesia in facial or nasal surgery.

Facial surgery may also be performed by local anaesthetic infiltration [5, 6]. However, regional nerve blocks have advantages over infiltration for facial anaesthesia because there is less tissue swelling at the operative site [5]. Some operations performed in our study could have been undertaken with simple packing of the nose with local anaesthetic agents. However, in our experience, anaesthesia produced by simple packing does not allow surgery on deep tissues without severe discomfort even if the patient is also sedated. In emergency cases, infiltration anaesthesia is satisfactory for small clean wounds of the face, but injection of local anaesthetics into or around dirty or macerated wounds, with the risk of distortion and damage of tissue, should be avoided. Furthermore, most of the patients treated as emergencies are assumed to have a full stomach, and regional anaesthesia in this context avoids the risk of general anaesthesia.

References

1. Bridenbaugh LD. Regional anaesthesia for outpatient surgery. *Canadian Anaesthetists Society Journal* 1983; **30**: 548–552.
2. Bonica JJ. General considerations of pain in the head. In: Bonica JJ, ed. *The Management of Pain*. Philadelphia: Lea & Febiger, 1990; 651–675.
3. Boberg-Ans J, Barner SS. Neural blockade for ophthalmologic surgery. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*. Philadelphia: JB Lippincott, 1980; 443–462.
4. Garber JG. Neural blockade for dental, oral, and adjoining areas. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*. Philadelphia: JB Lippincott, 1980; 426–442.
5. Kays CR. Local infiltration versus regional anesthesia of the face: case report and review. *Journal of the South Carolina Medical Association* 1988; **84**: 494–496.
6. Dicker RL, Syracuse VR. Local anesthesia in facial plastic surgery. *Otolaryngology* 1978; **86**: 461–467.

British Journal of Anaesthesia 1996; **76**: 154–155

Effect of smoking on dose requirements for vecuronium

H. Teiriä, P. Rautoma and A. Yli-Hankala

Summary

We have compared the potency of vecuronium given to 12 smokers and 12 non-smokers during propofol–alfentanil–nitrous oxide anaesthesia. After obtaining individual dose–response curves, bolus doses of vecuronium were given to maintain neuromuscular block at 90–98% for 60 min. Adductor pollicis EMG was used to monitor neuromuscular block. Mean ED_{95} values were 61.38 μg kg^{-1} and 47.49 μg kg^{-1} for smokers and non-smokers, respectively ($P < 0.01$). The dose of vecuronium to maintain 90–98% neuromuscular block was 25% higher in smokers than in non-smokers (96.80 *vs* 72.11 μg kg^{-1} h^{-1}; $P < 0.01$). These data reflect the effects of smoking on neuromuscular block induced by vecuronium. The effect may be at the receptor level, although possible increased metabolism of vecuronium in smokers cannot be excluded. (*Br. J. Anaesth.* 1996; **76**: 154–155)

Key words

Neuromuscular block, vecuronium. Complications, smokers.

Smoking changes the potency of many drugs [1]. The effect of smoking on the pharmacodynamics of neuromuscular blockers is poorly understood. A recent study suggested that cigarette smokers are more sensitive to atracurium than non-smokers, possibly because of down-regulation of receptors [2]. However, our clinical impression is that smokers seem to consume more vecuronium than non-smokers. Therefore, we designed a study to evaluate the effect of smoking on the pharmacodynamics of vecuronium.

Methods and results

The study was approved by the Ethics Committee of the hospital. All patients were white, ASA I–II. Twelve smokers (six female; median age 35 (range 19–49) yr; weight 69 (55–91) kg) and 12 non-smokers (eight female; median age 41 (20–47) yr; weight 65 (59–85) kg) gave informed consent. Exclusion criteria were: body weight index more than 27; any disease or medication known to affect neuromuscular block; and weekly alcohol consumption more than 20 units (1 unit = one drink, a glass of wine or a bottle of beer). Smokers inhaled more than 10 cigarettes per day.

Patients were premedicated with midazolam 15 mg orally. An antecubital vein was cannulated for i.v. infusion. Neuromuscular function was monitored by adductor pollicis EMG (Relaxograph, Datex/Instrumentarium, Finland). The stimulating surface electrodes were placed over the ulnar nerve, the recording electrode over the adductor pollicis muscle and the reference electrode on the proximal area of the second finger. The forearm and thumb were attached to a dorsal splint to maintain immobility. The hand was covered with an aluminium sheet to prevent cooling. Skin temperature of the hand was maintained at more than 33 °C.

Anaesthesia was induced with alfentanil 10–20 μg kg^{-1} and propofol 2–3 mg kg^{-1}, and maintained with an infusion of propofol 6–10 mg kg^{-1} h^{-1}, 66% nitrous oxide in oxygen and bolus doses of alfentanil up to 50 μg kg^{-1} h^{-1}. The neuromuscular monitor was calibrated after induction of anaesthesia and before administration of the neuromuscular blocker (supramaximal train-of-four stimulation, 2 Hz every 20 s). Calibration was continued until unchanged EMG responses were recorded for more than 2 min.

After calibration, the first dose of vecuronium 20 μg kg^{-1} was given. The ensuing block was monitored until stabilization. The ED_{95} for vecuronium was calculated by creating an individual dose–response curve. For this purpose, vecuronium was given according to the two-dose technique described previously [3]. Tracheal intubation was performed when the EMG response was $< 15\%$ of baseline. Neuromuscular block was maintained at 90–98% for 60 min by administering vecuronium boluses (20% of the estimated individual ED_{95} dose) when needed. The dose of vecuronium was recorded and calculated later. Analysis of variance, followed by Scheffe's *post hoc* test, was used to compare means. $P < 0.05$ was considered statistically significant.

The results of the study are presented in table 1. The response after the last individual incremental dose of vecuronium was 95–98% of maximum and it averaged 12.1 min (no significant difference between groups). Mean end-tidal carbon dioxide concentration was 5.04% (ns). Skin temperature averaged 34.8 °C (ns).

Helena Teiriä, md, Pekka Rautoma md, Arvi Yli-Hankala md, phd, Department of Anaesthesia, Helsinki University Central Hospital, Haartmaninkatu 4, FIN-00290 Helsinki, Finland.
Accepted for publication: August 1, 1995.
Correspondence to H.T.

Table 1 Mean (95% confidence limits) values of hourly consumption of vecuronium (Cons), slope of the dose–response (Slope), ED_{95} and ED_{95}/hourly consumption of vecuronium (Ratio) between smokers and non-smokers. $^{**}P < 0.01$ between groups (ANOVA and Scheffe's test).

	Smokers	Non-smokers
Cons ($\mu g\ kg^{-1}\ h^{-1}$)	96.80** (88.49, 105.10)	72.11 (64.46, 79.77)
Slope (probit $\log^{-1}$)	6.48 (5.66, 7.29)	7.33 (5.80, 8.86)
ED_{95} ($\mu g\ kg^{-1}$)	61.38** (53.27, 69.49)	47.49 (42.16, 52.82)
Ratio	1.65 (1.43, 1.87)	1.53 (1.37, 1.68)

Comment

Our study suggested that smokers are more resistant to vecuronium than non-smokers. The site of this action is not clear. Both ED_{95} values and the hourly consumption of vecuronium were increased in smokers. Increased ED_{95} values probably reflect altered pharmacodynamics at the receptor site. Increased hourly consumption of vecuronium may indicate either increased plasma concentration of the drug, i.e. increased requirement of vecuronium at the receptor site to maintain neuromuscular block, or increased metabolism. The ED_{95}/consumption ratio of vecuronium did not differ between groups, nor did the slopes of the dose–response curves. The similar slopes of the dose–response curves may indicate that the metabolism of vecuronium during construction of the dose–response curve did not differ between groups.

Small doses of nicotine (< 100 ng ml^{-1}) stimulate the neuromuscular junction directly (acetylcholine-like action) and facilitate transmission of impulses. Larger doses ($> 10\ \mu g\ ml^{-1}$) block transmission because of persistent depolarization (acute effect) or desensitization of the receptor site (chronic effect) [4]. Based on the routine procedures of our hospital, patients were not allowed to smoke for 6 h before anaesthesia. Even heavy smoking does not increase blood nicotine concentrations to more than 75 ng ml^{-1} [5]. Low blood concentrations of nicotine might, therefore, partly explain our results. Tobacco smoke, however, is a mixture of more than 3000 different compounds [1]. It has enzyme-inducing properties; enhanced biotransformation of many drugs sharing the cytochrome P-450 mixed function oxidase pathway has been correlated with cigarette smoking [1]. Therefore, factors other than directly nicotine-induced mechanisms may play a role in increased resistance of vecuronium in smokers.

We measured the ED_{95} for vecuronium over a period of 12 min. If metabolism of vecuronium were increased, this relatively long measurement time might result in inaccurately increased ED_{95} values in smokers [6]. Our measurement method was therefore not ideal. However, the difference in ED_{95} value between smokers and non-smokers was more than 20%. This probably cannot be explained solely by increased metabolism of the drug. An altered mechanism of action on the neuromuscular junction may also be involved therefore.

In the report of Kroeker, Beattie and Yang [2], smokers appeared to require less atracurium than non-smokers. This contrasts with the results presented here. More studies are needed to elucidate the mechanism of the effects of cigarette smoking on the neuromuscular junction and clarify this difference.

References

1. Dawson GW, Vestal RE. Smoking and drug metabolism. *Pharmacology and Therapeutics* 1982; **15**: 207–221.
2. Kroeker KA, Beattie WS, Yang H. Neuromuscular blockade in the setting of chronic nicotine exposure. *Anesthesiology* 1994; **81**: A1120.
3. Meretoja OA, Wirtavuori K. Two-dose technique to create an individual dose–response curve for atracurium. *Anesthesiology* 1989; **70**: 732–736.
4. Taylor P. Agents acting at the neuromuscular junction and autonomic ganglia. In: Goodman Gilman A, Rall TW, Nies AS, Taylor P, eds. *The Pharmacological Basis of Therapeutics, vol. 1*. New York: McGraw Hill Inc., 1992; 166–186.
5. Russell MAH, Jarvis M, Iyer R, Feyerabend C. Relation of nicotine yield of cigarettes to blood nicotine concentrations in smokers. *British Medical Journal* 1980; **280**: 972–975.
6. Gibson FM, Mirakhur RK, Clarke RSJ, Lavery GG. Comparison of cumulative and single bolus dose techniques for determining the potency of vecuronium. *British Journal of Anaesthesia* 1985; **57**: 1060–1062.

British Journal of Anaesthesia 1996; **76**: 156–159

CASE REPORTS

Airway problems after carotid endarterectomy

F. J. MUNRO, A. P. MAKIN AND J. REID

Summary

Respiratory obstruction has been reported as a complication of carotid endarterectomy; the causes include traumatic mucosal oedema, direct tracheal compression by haematoma and oedema secondary to lymphatic and venous congestion. We report four cases of acute respiratory obstruction complicating carotid endarterectomy. Two of these cases suffered respiratory arrest in the postoperative ward and required emergency tracheal intubation in difficult circumstances. All of these patients had developed wound haematomas and all required surgical intervention. (*Br. J. Anaesth.* 1996; **76**: 156–159)

Key words

Surgery, endarterectomy. Airway, obstruction. Complications, airway obstruction.

Carotid endarterectomy is of proven efficacy in moderate to severe carotid artery stenosis [1]. Surgery involves a vascular graft and manipulation of the carotid body. Recognized complications include postoperative hyper- or hypotension, wound haemorrhage, local oedema and neurological deficits [2]. Airway obstruction is well recognized; this may be caused by haematoma formation, oedema or a combination of both [3]. During a 1-yr period in our unit when 100 procedures were performed, there were four cases of haematoma leading to a compromised airway which required acute airway management and surgical intervention.

Case reports

PATIENT NO. 1

A 71-yr-old male was admitted for left carotid endarterectomy having suffered a cerebrovascular accident 10 months previously. His past medical history included hypertension and ischaemic heart disease treated with aspirin, nifedipine and bendrofluazide. His preoperative arterial pressure was 180/90 mm Hg. The operation was uneventful. Throughout the procedure the patient had a stable cardiovascular system and an arterial cannula was used to monitor arterial pressure. According to our standard routine management, heparin 3000 u. was administered i.v. and reversed later with protamine 30 mg i.v. After operation, in the recovery unit, invasive arterial pressure monitoring was continued. Recovery was complicated by systolic hypertension which was treated with increments of hydralazine i.v., however, a systolic arterial pressure of 260 mm Hg was reached before control was achieved.

A neck haematoma was first noticed 1 h from completion of the procedure. At this time the patient's coagulation profile was normal. The haematoma continued to expand and 5 h after operation the patient was noted to be hoarse. On examination there was no respiratory distress and the trachea was central. The patient was reviewed by the vascular surgeon and the area of haematoma was marked. One hour later, with no further evidence of enlargement of the neck swelling, the patient was transferred to the postoperative surgical ward where invasive arterial pressure monitoring was discontinued. Nine hours after operation the patient became acutely dyspnoeic and developed stridor. This progressed rapidly to complete airway obstruction and respiratory arrest. At laryngoscopy no normal structures were seen, the soft tissues were grossly oedematous and friable, with fresh bleeding on pharyngeal suction. Intubation was achieved blindly with a 6.0-mm tracheal tube via the right side of the pharynx. The patient was sedated, paralysed and transferred to the operating theatre where a large haematoma was evacuated. The left facial vein was identified as the source of bleeding and was ligated. Small bleeding points were also sutured on the arterial vein patch. Before tracheal extubation was attempted a gum elastic bougie was inserted. The tracheal tube was then removed and laryngoscopy showed the larynx to be central with both vocal cords moving normally. After removal of the bougie there was no stridor.

Haemoglobin concentration decreased from 13.3 g dl^{-1} before operation to 9.9 g dl^{-1}. The patient made a full recovery and was discharged on day 5 after operation with no neurological deficit.

PATIENT NO. 2

A 72-year-old male was admitted for left carotid endarterectomy having suffered multiple transient ischaemic attacks in the preceding months. He had a

---

FIONA J. MUNRO, FRCA, ANDREW P. MAKIN, FFARCSI, FRCA, JOYCE REID, FRCA, Department of Anaesthesia, Western Infirmary, Dumbarton Road, Glasgow G11 6NT. Accepted for publication: August 14, 1995.

history of hypertension. His treatment consisted of aspirin, bendrofluazide, atenolol and diltiazem. Preoperative arterial pressure was 170/68 mm Hg. The operation was uneventful. Intraoperatively heparin 3000 u. i.v. was administered and reversed later with protamine 30 mg, i.v.

After operation, in the recovery unit, he developed hypertension, peaking at 220/130 mm Hg, despite early treatment with bolus doses of i.v. hydralazine. Neck swelling was first noted 30 min after operation; however, after regular surgical review in the recovery unit it was decided to pursue conservative management. With arterial pressure stable and no apparent further increase in haematoma size, the patient was transferred to the surgical ward. Here, after 8 h, the patient developed acute respiratory embarrassment leading to respiratory arrest. At laryngoscopy no anatomical structures could be identified and the trachea was intubated blind with a 7.5-mm tracheal tube through swollen mucosal folds. The patient was then transferred to the intensive care unit. On return to theatre the following morning a large haematoma was evacuated and a bleeding point on a branch of the internal jugular vein ligated. Tracheal extubation 4 h later was uneventful. His haemoglobin concentration decreased from 13 to 9.6 g dl^{-1} and required transfusion of 2 u. of packed red cells. Postoperative recovery was complicated by transient right-sided weakness and dysphasia which resolved before discharge on day 7 after operation.

PATIENT NO. 3

A 79-yr-old male was admitted for right carotid endarterectomy. He had suffered several transient ischaemic attacks in the preceding months and had a history of treated hypothyroidism. His regular medication consisted of aspirin, propranolol and thyroxine. Preoperative arterial pressure was 160/70 mm Hg. The operation was complicated by low stump occlusion pressure, difficulty in inserting the Javed shunt and oozing from the vein graft, requiring extra sutures. Heparin 3000 u. i.v. was administered and reversed later with protamine 30 mg i.v. In the recovery unit a systolic pressure of 220 mm Hg was recorded 6 h after operation which was treated promptly with i.v. hydralazine. At this time the patient was agitated, hoarse and had developed a wound haematoma. He was reviewed by the surgeon at this time and it was decided to manage the patient conservatively on the postoperative surgical ward. At 10 h after operation he had developed stridor and was therefore returned urgently to theatre.

A rapid sequence induction was performed with etomidate 8 mg, midazolam 2.5 mg and suxamethonium 100 mg. Initially at laryngoscopy no normal structures could be identified because of the grossly distended pharyngeal veins and oedematous soft tissues. On further manipulation, the larynx was seen deviated to the far left of the pharynx. Intubation was then accomplished with an 8.5-mm tracheal tube. At operation a large haematoma was evacuated and haemostasis was produced with sutures to the vein graft. After operation he was transferred to ITU and the trachea extubated uneventfully within a few hours. His preoperative haemoglobin concentration of 11.2 g dl^{-1} decreased to 7.6 g dl^{-1} after operation. His recovery was complicated by a transient hemiparesis and cerebellar signs which resolved before discharge.

PATIENT NO. 4

A 56-yr-old male was admitted for left carotid endarterectomy. He had suffered several transient ischaemic attacks in the previous 6 months and was receiving regular aspirin treatment. He had no other significant medical history. Preoperative arterial pressure was 130/80 mm Hg. At operation a Javed shunt was inserted and standard anticoagulation and reversal administered. In the recovery unit he developed systolic hypertension of 210 mm Hg which was treated successfully with sublingual nifedipine. At this time he was noted to be hoarse and had developed a neck haematoma. He remained in the recovery unit and was reviewed by the surgeon who considered surgical intervention unnecessary. Before transfer to the surgical ward, the haematoma was unchanged in appearance for longer than 1 h, with minimal drainage.

At 6 h after operation in the surgical ward, the neck swelling had progressed and it was decided to explore the wound. On assessment of the airway there was limited mouth opening as a result of gross neck swelling. An inhalation induction was performed with oxygen, nitrous oxide and enflurane. As the airway was easy to maintain, etomidate 12 mg and suxamethonium 100 mg were administered. Intubation was straightforward with a 9.0-mm tracheal tube. At operation a large haematoma was removed, a small artery was cauterized and a defect in the left facial vein sutured. Tracheal extubation immediately after operation was uneventful. His preoperative haemoglobin concentration decreased from 13.9 to 12 g dl^{-1}. He was discharged home on day 4 after operation with no neurological deficit.

Discussion

Previous reports have postulated that the aetiology of airway obstruction after carotid endarterectomy surgery may be direct tracheal compression by haematoma, oedema secondary to either direct mucosal trauma or lymphatic and venous congestion resulting from haematoma formation [4, 5]. Reports suggesting oedema as the primary causal factor have described evacuation of haematoma which did not immediately relieve the airway obstruction; indeed 10 h of elective ventilation after operation has been recommended [6]. Dexamethasone has also been recommended prophylactically after prolonged neck surgery for this reason [7]. However, evacuation of haematoma has also been reported to relieve airway obstruction immediately [8].

Among the four cases described here, there were striking similarities in the perioperative events, which may have contributed to the development of similar postoperative complications. All patients were receiving aspirin as antiplatelet therapy which theoretically may have resulted in impaired clot formation, aggravating any bleeding. Also, they all received i.v. anticoagulation during operation, although this was reversed adequately with i.v. protamine.

Despite continuous arterial pressure monitoring and the presence of a recovery anaesthetist, postoperative hypertension was common to all cases in the first 6 h. This was controlled successfully with either hydralazine or nifedipine and may have contributed to arterial bleeding but would not account for haematoma formation caused by venous bleeding. Hypertension is well recognized after carotid endarterectomy; it may be caused by carotid body stimulation, pain or neurological insult. Urgent treatment of such severe hypertension is imperative in order to avoid cerebral haemorrhage. When using i.v. vasodilator therapy the dose must be titrated to effect in order to avoid myocardial or neurological damage caused by inadvertent hypotension.

In all cases, the neck haematomas were large and associated with a decrease in haemoglobin (1.9–3.6 g dl^{-1}). All patients were reviewed by vascular surgeons who, in the absence of airway difficulties and no further neck swelling, considered surgical intervention inappropriate.

Of these patients, three subsequently developed hoarseness but only in one case was evacuation of the haematoma carried out when minimal airway distress was present. In the other two cases conservative management continued until surgery was prompted by respiratory arrest when gross anatomical distortion was found at laryngoscopy. At exploration definite venous bleeding points were identified in three cases; two of these were also bleeding from the arterial vein patch.

It is of interest that in the four cases presented, in two the trachea was extubated at the end of the procedure and in one at 4 h after operation without complications. The fourth was transferred to the regional intensive care unit where evacuation of haematoma was scheduled for the next day and the trachea was extubated 4 h after operation.

Of the three mechanisms of airway obstruction described above, we suggest that haematoma causing lymphatic and venous congestion leading finally to oedema was the most likely sequence of events. This is supported by the delayed onset of airway obstruction and the rapid resolution of oedema after evacuation of the haematoma facilitating early tracheal extubation after operation.

In the emergency situation the airway may be difficult to assess and the degree of expected difficulty is often not fully appreciated. The final life-threatening deterioration is frequently rapid with little warning. Stridor appears to present late as a clinical sign. However, subtle changes in voice quality progressing to hoarseness in the presence of such acute neck swelling should be treated as an indication of impending airway obstruction. In the above cases developing haematoma was initially managed conservatively (6–10 h) before intervention. It is of concern that two of these patients suffered respiratory arrest and in both the trachea was intubated blindly on the ward under difficult conditions.

In order to avoid the catastrophic consequences of respiratory arrest from a completely obstructed airway we suggest that progressive neck swelling should be managed aggressively with early surgical intervention. Successful evacuation of such haematomas under local anaesthesia has been reported. Also, after extensive neck surgery patients should be managed in a high dependency unit with appropriate monitoring, levels of nursing staff and the immediate availability of anaesthetic expertise.

In the event of airway obstruction, management strategies that have been documented include inhalation induction, with or without helium, to decrease turbulent airflow. Fibreoptic intubation has also been advocated, although this technique required a skilled operator and vision may be impaired by anatomical distortion, venous congestion and secretions. Also, the smallest tracheal tube accommodated by the standard intubating bronchoscope is 6.5 mm which may be difficult to pass. Both the retrograde intubation technique and the creation of a surgical airway may be difficult and extremely dangerous in the swollen neck.

It is of concern that anaesthesia was induced in one patient with a rapid sequence induction resulting in unexpected difficulty in seeing the larynx. Fortunately, there were no long-term sequelae as a result of this delay in securing the airway. However, in a previous report of six similar cases, four of which were initially paralysed resulting in inability to ventilate the lungs, all suffered severe hypoxia and cardiac arrhythmias [4]. In three of these the trachea was intubated with difficulty using small tracheal tubes and one underwent emergency tracheostomy while asystolic.

The appropriate moment for extubation may be difficult to assess. From our experience it would seem that elective postoperative ventilation is not always necessary. Various methods may assist in assessing the ability to extubate the trachea successfully at the end of the procedure, namely an audible leak around the deflated cuff at 15 cm H_2O of airway pressure or leaving a gum elastic bougie or a Cooke airway exchanger *in situ* after removal of the tracheal tube.

All patients recovering from carotid endarterectomy require high dependency care to ensure continuous assessment of respiratory and cardiovascular systems. In our unit there is a planned upgrading of the postoperative surgical ward to high dependency status.

References

1. Garrioch MA, Fitch W. Anaesthesia for carotid artery surgery. *British Journal of Anaesthesia* 1993; 71: 569–579.
2. Bjoraker DG. Abdominal and major vascular surgery. In: Nimmo WS, Smith G, eds. *Anaesthesia.* Oxford: Blackwell Scientific Publications, 1989; 740–743.
3. Randalls B, Toomey PJ. Laryngeal oedema from neck haematoma. *Anaesthesia* 1990; 45: 850–852.
4. O'Sullivan JC, Wells DG, Wells GR. Difficult airway management with neck swelling after carotid endarterectomy. *Anaesthesia and Intensive Care* 1986; 14: 460–464.

5. Wade JSH. Respiratory obstruction in thyroid surgery. *Annals of the Royal College of Surgeons of England* 1980; **62**: 15–24.
6. Bexton MDR, Radford RM. An unusual cause of respiratory obstruction after thyroidectomy. *Anaesthesia* 1982; **37**: 596.
7. Cox C, Bannister B. Anaesthesia for carotid artery surgery. *British Journal of Anaesthesia* 1994; **74**: 252.
8. Bukht D, Langford RM. Airway obstruction after surgery in the neck. *Anaesthesia* 1983; **38**: 389–390.

British Journal of Anaesthesia 1996; **76**: 160–162

Mivacurium chloride and late onset congenital myopathy

M. PARMAR AND R. P. F. SCOTT

Summary

We describe the successful use of the short-acting, non-depolarizing neuromuscular blocking agent, mivacurium, in a 53-yr-old female patient with late onset congenital myopathy, undergoing elective submucous resection of the inferior turbinates. She was unable to climb stairs and walking was limited to periods of 15 min because of generalized weakness, fatigue and shortness of breath. A Datex Relaxograph was used to monitor the train-of-four count. No increase in sensitivity to mivacurium was demonstrated. A dose of 12 mg (three times the recommended ED_{95}) resulted in 88% reduction of the first of the train-of-four count (T1) compared with control (TC). Spontaneous recovery of T1/TC to 100% took 11 min 20 s from the time maximum block was first achieved. The recovery index (25–75% T1/TC) was 4 min 40 s. (*Br. J. Anaesth.* 1996; **76**: 160–162)

Key words

Neuromuscular block, mivacurium. Complications, myopathy.

Abnormal responses to neuromuscular block are well recognized in several muscle disorders [1–4]. Late onset congenital myopathy presents in adulthood with a gradual generalized weakness of not only the limb muscles but also the respiratory muscles. Little is known about the effect of neuromuscular block in patients with congenital myopathy. The few cases that are reported describe the use, without complications, of normal doses of the long-acting neuromuscular blocking agent, pancuronium, in patients who presented in childhood with this condition [5, 6]. We are unaware of any previously reported use of the short acting neuromuscular blocking drug, mivacurium, in patients with adult onset congenital myopathy.

Case report

MEDICAL HISTORY

A 53-yr-old female patient, weighing 50 kg, height 177 cm, presented for elective submucous resection of the inferior turbinates. She had a long history of muscle weakness dating back to adolescence when she found that she had difficulty keeping her arms above her head for any period of time. In her late twenties she had difficulty climbing stairs and more recently was unable to do so. She used crutches to walk but was limited to periods of 15 min because of generalized weakness, fatigue and shortness of breath. She wore a neck collar continuously as the weakness in her neck caused her head to droop. There was no specific difficulty with swallowing and no diplopia. She had no muscle weakness during childhood.

Her other past medical history revealed that she had developed osteoporosis in her forties and had been receiving hormone replacement therapy. She also suffered from dyspepsia for which she received omeprazole and cisapride. There was no family history of muscle disorders and she was a non-smoker.

CLINICAL EXAMINATION

She was a thin lady with no signs of cardiac or respiratory failure. There was wasting of the deltoid, glutei and to a lesser extent the quadriceps muscles. She was unable to abduct her arms beyond 90° offering only mild resistance to forced adduction. There was mild weakness of hip flexion and leg extension such that movement against gravity and mild resistance to force were possible but not sustained. Reflexes were symmetrical with a negative plantar reflex. Cranial nerve examination was normal.

INVESTIGATIONS

Full blood count, urea, creatinine and other electrolyte concentrations were normal, including serum creatine kinase. Electrocardiography and chest x-ray were normal. Lung function tests performed before operation showed a peak expiratory flow rate of 380 litre min^{-1} (80% of predicted). Forced vital capacity (FVC) was 1.88 litre (52% of predicted). FEV_1 was 1.85 litre (60% of predicted) with FEV_1/FVC 98%. Maximal pressures generated at the mouth, after full inspiration and full expiration, that is maximal expiratory and maximal inspiratory pressures, were measured using a mouth pressure meter (Precision Medical, Pickering, Yorks, UK). These were 26% and 36% of predicted, respectively, reflecting global respiratory muscle weakness. Carbon monoxide transfer tests were within normal limits. Nerve conduction studies were normal and a previous electromyograph showed myopathic changes. A

M. PARMAR*, BSC, MB, BS, MRCP, FRCA, R. P. F. SCOTT, BSC, MB, CHB, FRCA, MD, Department of Anaesthetics, Salisbury District Hospital, Salisbury, Wiltshire SP2 8BJ. Accepted for publication: September 5, 1995.

*Address for correspondence: Department of Anaesthetics, Southampton General Hospital, Tremona Road, Southampton SO9 4XY.

quadriceps muscle biopsy showed generalized widespread mild degenerative changes with selective type 2B fibre atrophy and a predominance of type 1 fibres. These changes were indicative of a non-specific congenital myopathy.

ANAESTHESIA

We were concerned that the patient would experience difficulty in breathing and prove to be a weaning problem after operation as a consequence of her generalized respiratory muscle weakness. Initial anaesthetic management therefore included pre-operative chest physiotherapy and breathing exercises and we ensured the availability of an intensive care bed.

Anaesthesia was induced with propofol 2 mg kg^{-1} and fentanyl 1 μg kg^{-1}. Anaesthesia was maintained initially with incremental doses of propofol with 66 % nitrous oxide in 34 % oxygen and the patient's breathing was assisted with a face mask at this stage.

Monitoring comprised electrocardiography, non-invasive arterial pressure, pulse oximetry, capnography and vapour analysis. The skin over the non-dominant forearm and hand was degreased using an alcoholic solution. Five silver–silver chloride electrodes were placed: two over the ulnar nerve, one over the mid-point of the distal skin crease at the wrist, one over the palmar aspect of the head of the first metacarpal and one over the belly of the adductor pollicis muscle. These were connected to a Datex Relaxograph. Neuromuscular monitoring was commenced using train-of-four (TOF) stimuli (2 Hz at 20-s intervals) to the ulnar nerve and the gated, rectified and integrated electromyograph from the adductor pollicis was recorded. A normal TOF trace was obtained. The size of the gain setting, supramaximal stimulus and the stimulus artefact were noted.

As the patient had muscle weakness, only a small dose (1 × ED_{95}) of mivacurium was administered. No effect on the TOF was seen after 4 min and therefore an additional dose of 4 mg was given. This resulted in a gradual reduction in the first twitch of the TOF (T1) which stabilized to a T1 response of 50 % compared with control (TC). Intubation was attempted with a cuffed tracheal tube size 8 mm at this stage but was unsuccessful because of difficulty in seeing the vocal cords. Another dose of mivacurium 4 mg was therefore administered 8 min after the first dose, which resulted in a decrease in T1/TC to 12 %. At this point the intubating conditions were much improved and the trachea was intubated. Maximum block of 88 % was achieved 12 min after the first dose of mivacurium had been given. The patient was taken into theatre and her lungs ventilated with 66 % nitrous oxide and 0.5 % enflurane in oxygen.

The cardiovascular system was stable and she remained normothermic throughout surgery. Additional mivacurium was not required and neuromuscular block was allowed to recover spontaneously. Recovery of T1/TC to 100 % took 11 min 20 s from the time maximum block was first achieved, with a recovery index (25–75 % T1/TC) of 4 min 40 s. Antagonism of neuromuscular block was not deemed necessary as the TOF ratio had recovered spontaneously to 1.0. The patient emerged from anaesthesia breathing spontaneously and the trachea was extubated uneventfully. Before extubation, the patient demonstrated good hand grip strength. In view of her myopathy, head lift testing was inappropriate. The postoperative period was unremarkable.

Discussion

The congenital myopathies are a rare and complex group of inherited muscle disorders which are associated with enzyme defects and structural abnormalities in the muscle fibres. Mitochondrial oxidative enzyme activity is reduced or absent in central core and multicore congenital myopathies [7–9]. The presence of abnormal muscle cell organelles such as rods and nemaline bodies characterize nemaline myopathy while abnormal nuclei are found in centronuclear myopathy [10]. In addition to the enzyme defects there is also heterogeneity of muscle fibre sizes, and atrophy or predominance of certain muscle fibres. In some patients it may be difficult to assign a specific diagnostic group as the muscle biopsy exhibits only non-specific changes and it must be noted that the cytoarchitectural changes and clinical severity may not correlate.

Most patients with congenital myopathy present in childhood. Generalized hypotonia may be detected as early as the neonatal period and delayed motor milestones are common. The child thus has difficulty in getting up from the floor, walking and later running and climbing stairs. There may be associated skeletal abnormalities such as scoliosis, pes cavus, clubbed feet or congenital hip dislocation [11]. Most cases are non or very slowly progressive; indeed, there may be early improvement in childhood but with varying degrees of subsequent deterioration [12]. The involvement of the respiratory muscles may cause respiratory failure which represents a common cause of death [5, 13].

Late onset congenital myopathies present in adulthood with gradual onset of mild muscle weakness involving proximal or distal muscle groups but eventually becoming generalized [14, 15]. As with the childhood disease, they are generally non or very slowly progressive and respiratory muscle paresis causing respiratory failure may be a contributory factor to death [16].

Our patient had a slow, progressive, disabling condition for which there was objective evidence of generalized muscle weakness. Of particular concern was the global respiratory muscle weakness, as suggested by assessment of peak inspiratory and peak expiratory mouth pressures. Failure to ventilate adequately and cough in the postoperative period may cause sputum retention and areas of lung collapse. Infection and hypoxia may supervene causing prolonged recovery and possibly even death. Fortunately our patient suffered none of these complications.

There is a predisposition to malignant hyperthermia during general anaesthesia in patients with central core congenital myopathy, particularly if associated with a raised creatine kinase concentration [17]. Muscle biopsy showed none of the features diagnostic of this type of congenital myopathy and our patient did not have a raised serum creatine kinase concentration. We therefore felt justified at the time in using a volatile agent. The importance of excluding risk factors must however be stressed before using known triggering agents of malignant hyperpyrexia in patients with muscle weakness.

Mivacurium chloride is a bis-benzylisoquinolonium diester neuromuscular blocking drug. It was selected because of its relative short duration of action. This characteristic seemed desirable as there was concern that this patient may exhibit particular sensitivity to neuromuscular block. After a single dose of $1 \times ED_{95}$, a greater than 90 % reduction in T1 compared with TC would be expected after 4 min [18]. Satisfactory intubating conditions, however, were not achieved in our patient until a total of $3 \times ED_{95}$ had been administered over 12 min. Recovery to 95 % T1/TC would be expected to take 30 min, with a recovery index of 7 min after a single bolus dose of $3 \times ED_{95}$ [18]. In our patient, recovery of T1/TC to 100 % took 23 min 20 s from the end of the first dose with a recovery index of 4 min 40 s. No unusual sensitivity to neuromuscular block with mivacurium was therefore demonstrated in our patient. Indeed, it could be argued that the patient showed some resistance to block but as the drug was given cumulatively it is more likely that some hydrolysis of the agent had occurred between increments.

Patients with neuromuscular disorders have a very variable response to neuromuscular blocking drugs. It is thus important to monitor neuromuscular function accurately in all such patients. We have described the safe and satisfactory use of mivacurium chloride in a patient with late onset congenital myopathy. However, we cannot on the basis of one patient suggest that all similar cases will necessarily have no complications, nor can we advocate an advantage in the use of mivacurium compared with other intermediate neuromuscular blocking agents.

References

1. Seigne RD, Scott RPF. Mivacurium chloride and myasthenia gravis. *British Journal of Anaesthesia* 1994; **72**: 468–469.
2. Eisenkraft JB, Book WJ, Papatestas AE. Sensitivity to vecuronium in myasthenia gravis: a dose–response study. *Canadian Journal of Anaesthesia* 1990; **37**: 301–306.
3. Churchill-Davidson HJ. Abnormal response to muscle relaxants. *Proceedings of the Royal Society of Medicine* 1955; **48**: 621–624.
4. Russell SH, Hirsch NP. Anaesthesia and myotonia. *British Journal of Anaesthesia* 1994; **72**: 210–216.
5. Asai T, Fujise K, Uchida M. Anaesthesia for cardiac surgery in children with nemaline myopathy. *Anaesthesia* 1992; **47**: 405–408.
6. Heard SO, Kaplan RF. Neuromuscular blockade in a patient with nemaline myopathy. *Anesthesiology* 1983; **59**: 588–590.
7. Mendell JR, Griggs RC. Inherited, metabolic, endocrine and toxic myopathies: congenital myopathies. In: Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL, eds. *Harrison's Principles of Internal Medicine*. New York: McGraw-Hill Inc, 1994; 2387.
8. Myong NH, Kang YK, Chi JG, Suk SI. Mulicore myopathy—a case report. *Journal of Korean Medical Science* 1993; **8**: 312–317.
9. Myong NH, Suh YL, Chi JG, Hwang YS. Central core disease—a case report. *Journal of Korean Medical Science* 1993; **8**: 235–240.
10. Gibbels E, Kellerman K, Schadlich HJ, Adams R, Haupt WF. Follow-up studies in a case of unusual congenital myopathy, suggestive of nemaline type. *Acta Neuropathologica* 1992; **83**: 371–378.
11. Disorders of muscle: The floppy infant syndrome. In: Sir John Walton, ed. *Brain's Diseases of the Nervous System*. Oxford Medical Publications, 1985; 582–584.
12. Shishikura K, Osawa M, Suzuki H, Hirayama Y, Arai Y, Sumida S, Takahashi R, Fukuyama Y. Clinical variability of congenital myopathy with type 1 fibre atrophy: a long term observation of three cases. *Acta Paediatrica Japonica* 1994; **36**: 186–193.
13. Sandler DL, Burchfield DJ, McCarthy JA, Rojiani AM, Drummond WH. Early-onset respiratory failure caused by severe congenital neuromuscular disease. *Journal of Pediatrics* 1994; **124**: 636–638.
14. Halbig L, Goebel HH, Hopf HC, Moll R. Spheroid–cytoplasmic complexes in a congenital myopathy. *Revue Neurologique* 1991; **147**: 300–307.
15. Brownell AKW, Gilbert JJ, Shaw DT, Garcza B, Wenkebach GF, Lam AKS. Adult onset nemaline myopathy. *Neurology* 1978; **28**: 1306–1309.
16. Rimmer KP, Whitelaw WA. The respiratory muscles in multicore myopathy. *American Review of Respiratory Disease* 1993; **148**: 227–231.
17. Eng GD, Epstein BS, Engel WK, McKay DW, McKay R. Malignant hyperthermia and central core disease in a child with congenital dislocating hips. Case presentation and review. *Archives of Neurology* 1978; **35**: 189–197.
18. Savarase JJ, Ali HH, Basta SJ, Embree PB, Scott RPB, Sunder N, Weakly JN, Wastila WB, El-Sayad HA. The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U): a short acting non-depolarizing ester neuromuscular blocking drug. *Anesthesiology* 1989; **71**: A825.

British Journal of Anaesthesia 1996; **76**: 163–166

Anaesthesia and juvenile hyaline fibromatosis

B. NORMAN, N. SONI AND N. MADDEN

Summary

Juvenile hyaline fibromatosis is a rare autosomal recessive disease characterized by large cutaneous nodules, especially around the head and neck and often involving the lips. The effects become increasingly severe with age and also include joint contractures, gingival hypertrophy and osteolytic lesions. We describe the anaesthetic management of two sisters with this disease. Safe maintenance of a patent airway is the principal anaesthetic challenge. (*Br. J. Anaesth.* 1996, **76**: 163–166)

Key words

Anaesthesia, paediatric. Complications, juvenile hyaline fibromatosis.

Two sisters with juvenile hyaline fibromatosis (JHF) presented for surgery several times at our hospital. The older sister had received her first anaesthetic at 14 months of age and subsequently had three further anaesthetics. On each occasion management of the airway had become more difficult. The younger sister had received one anaesthetic at 2 yr of age when tracheal intubation was relatively easy.

For both sisters other aspects of anaesthesia and postoperative care were straightforward. For each anaesthetic they were premedicated with EMLA cream and atropine 20 μg kg^{-1} i.m. Despite the presence of joint contractures, venous cannulation was performed successfully. When the airway was secured, the lungs were easy to ventilate with normal airway pressures and oxygenation. With the exception of the elder sister's second anaesthetic, when surgery was of short duration and a laryngeal mask was used, the sisters were given atracurium 0.5 mg kg^{-1} i.v. and the lungs ventilated. The patients remained in a stable cardiovascular state during anaesthesia. After anaesthesia the trachea was extubated with the patients awake without difficulty and they required only mild postoperative analgesia.

Case reports

PATIENT NO. 1

The older sister had her first anaesthetic at 14 months of age to enable tissue biopsies to be performed. At that age she already had very abnormal facies with polyploid masses around the mouth and limited mouth opening. She also had large irregular growths on her head and back so that padding with soft packing material was required to position her for anaesthesia and surgery. Anaesthesia was induced with oxygen and halothane, and suxamethonium 1 mg kg^{-1} was given i.v. and her trachea intubated without difficulty. Her subsequent anaesthetic was uneventful.

At 20 months of age she presented for further tissue biopsies. Anaesthesia was induced with oxygen and halothane and maintained with spontaneous breathing. Laryngoscopy was performed under deep halothane anaesthesia to assess the difficulty of intubation. It was impossible to view the epiglottis as the jaw, tongue and pharynx were infiltrated and rigid. A size 2 laryngeal mask was inserted with some difficulty; the mouth opened sufficiently to admit the mask but it took several attempts to pass it downwards behind the tongue. After insertion the laryngeal mask was used to maintain the airway with spontaneous ventilation for the remainder of the anaesthetic.

At 3 years 3 months she presented for removal of lesions around her mouth and trimming of deposits on the trunk which were beginning to ulcerate. On examination she had a grossly abnormal face with marked protuberance of her maxilla caused by infiltrations (fig. 1). Her mouth was open and would admit one finger but the tissues in and around the mouth were rigid. Her lower jaw was hard with infiltrations. She had a good air flow through her right nostril. Anaesthesia was induced with oxygen and halothane. A size 3.0-mm tracheal tube was introduced gently into the right nostril and used as a nasal airway to maintain inhalation anaesthesia while examination with a fibreoptic intubating bronchoscope was performed via the left nostril. The left nasal passage was grossly abnormal and very narrow, with hyaline deposits throughout. The epiglottis was infiltrated and looked abnormal, as did the larynx which was narrowed. It was impossible to identify the arytenoids. Intubation was performed successfully by passing a 4.0-mm tracheal tube over the fibreoptic bronchoscope.

Five months later she again presented for anaesthesia for surgical treatment of sacral ulceration and extensive debridement of facial and mouth lesions. A computed tomography scan of the airway was obtained before operation and showed significant narrowing of the pharynx and trachea (figs 2, 3). The same anaesthetic technique was used as in the previous anaesthetic. The airway viewed with the

---

B. NORMAN*, FRCA, N. SONI, FANZCA, N. MADDEN, FRCS, Magill Department of Anaesthetics, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH. Accepted for publication: July 25, 1995.

*Present address for correspondence: Department of Anaesthetics, The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG.

British Journal of Anaesthesia 1996; **76**: 163–166

Anaesthesia and juvenile hyaline fibromatosis

B. NORMAN, N. SONI AND N. MADDEN

Summary

Juvenile hyaline fibromatosis is a rare autosomal recessive disease characterized by large cutaneous nodules, especially around the head and neck and often involving the lips. The effects become increasingly severe with age and also include joint contractures, gingival hypertrophy and osteolytic lesions. We describe the anaesthetic management of two sisters with this disease. Safe maintenance of a patent airway is the principal anaesthetic challenge. (*Br. J. Anaesth.* 1996, **76**: 163–166)

Key words

Anaesthesia, paediatric. Complications, juvenile hyaline fibromatosis.

Two sisters with juvenile hyaline fibromatosis (JHF) presented for surgery several times at our hospital. The older sister had received her first anaesthetic at 14 months of age and subsequently had three further anaesthetics. On each occasion management of the airway had become more difficult. The younger sister had received one anaesthetic at 2 yr of age when tracheal intubation was relatively easy.

For both sisters other aspects of anaesthesia and postoperative care were straightforward. For each anaesthetic they were premedicated with EMLA cream and atropine 20 $\mu g\ kg^{-1}$ i.m. Despite the presence of joint contractures, venous cannulation was performed successfully. When the airway was secured, the lungs were easy to ventilate with normal airway pressures and oxygenation. With the exception of the elder sister's second anaesthetic, when surgery was of short duration and a laryngeal mask was used, the sisters were given atracurium 0.5 $mg\ kg^{-1}$ i.v. and the lungs ventilated. The patients remained in a stable cardiovascular state during anaesthesia. After anaesthesia the trachea was extubated with the patients awake without difficulty and they required only mild postoperative analgesia.

Case reports

PATIENT NO. 1

The older sister had her first anaesthetic at 14 months of age to enable tissue biopsies to be performed. At that age she already had very abnormal facies with polyploid masses around the mouth and limited mouth opening. She also had large irregular growths on her head and back so that padding with soft packing material was required to position her for anaesthesia and surgery. Anaesthesia was induced with oxygen and halothane, and suxamethonium 1 $mg\ kg^{-1}$ was given i.v. and her trachea intubated without difficulty. Her subsequent anaesthetic was uneventful.

At 20 months of age she presented for further tissue biopsies. Anaesthesia was induced with oxygen and halothane and maintained with spontaneous breathing. Laryngoscopy was performed under deep halothane anaesthesia to assess the difficulty of intubation. It was impossible to view the epiglottis as the jaw, tongue and pharynx were infiltrated and rigid. A size 2 laryngeal mask was inserted with some difficulty; the mouth opened sufficiently to admit the mask but it took several attempts to pass it downwards behind the tongue. After insertion the laryngeal mask was used to maintain the airway with spontaneous ventilation for the remainder of the anaesthetic.

At 3 years 3 months she presented for removal of lesions around her mouth and trimming of deposits on the trunk which were beginning to ulcerate. On examination she had a grossly abnormal face with marked protuberance of her maxilla caused by infiltrations (fig. 1). Her mouth was open and would admit one finger but the tissues in and around the mouth were rigid. Her lower jaw was hard with infiltrations. She had a good air flow through her right nostril. Anaesthesia was induced with oxygen and halothane. A size 3.0-mm tracheal tube was introduced gently into the right nostril and used as a nasal airway to maintain inhalation anaesthesia while examination with a fibreoptic intubating bronchoscope was performed via the left nostril. The left nasal passage was grossly abnormal and very narrow, with hyaline deposits throughout. The epiglottis was infiltrated and looked abnormal, as did the larynx which was narrowed. It was impossible to identify the arytenoids. Intubation was performed successfully by passing a 4.0-mm tracheal tube over the fibreoptic bronchoscope.

Five months later she again presented for anaesthesia for surgical treatment of sacral ulceration and extensive debridement of facial and mouth lesions. A computed tomography scan of the airway was obtained before operation and showed significant narrowing of the pharynx and trachea (figs 2, 3). The same anaesthetic technique was used as in the previous anaesthetic. The airway viewed with the

---

B. NORMAN*, FRCA, N. SONI, FANZCA, N. MADDEN, FRCS, Magill Department of Anaesthetics, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH. Accepted for publication: July 25, 1995.

*Present address for correspondence: Department of Anaesthetics, The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG.

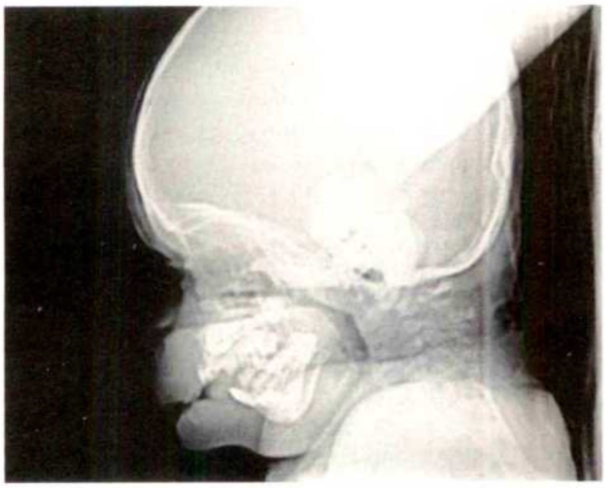


Figure 1 Lateral skull x-ray demonstrating marked soft tissue deposits adjacent to the mouth caused by juvenile hyaline fibromatosis.

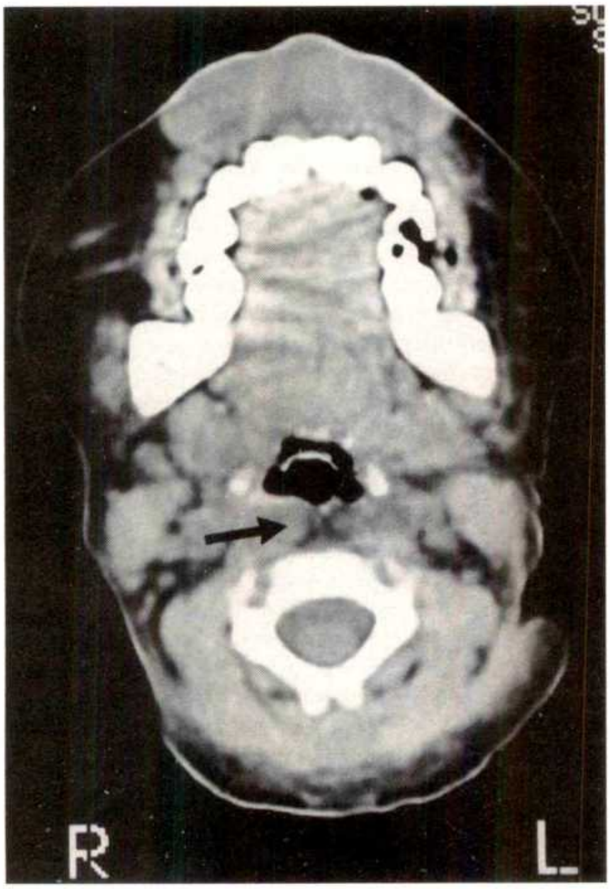


Figure 2 Computed tomography of the neck demonstrating narrowing of the pharynx. The thickening of soft tissues between the posterior pharyngeal wall and the cervical spine is marked by an arrow.

fibreoptic bronchoscope was much narrower and more tortuous than on the previous occasion. However, it did lead directly to the larynx. This was identified as a small black orifice which appeared and disappeared with breathing. There were no identifiable anatomical landmarks as these were obscured by hyaline deposits. It was clear that there had been significant progression of the infiltration since the last anaesthetic. As previously, intubation was achieved by passing a 4.0-mm tracheal tube over the fibreoptic bronchoscope.

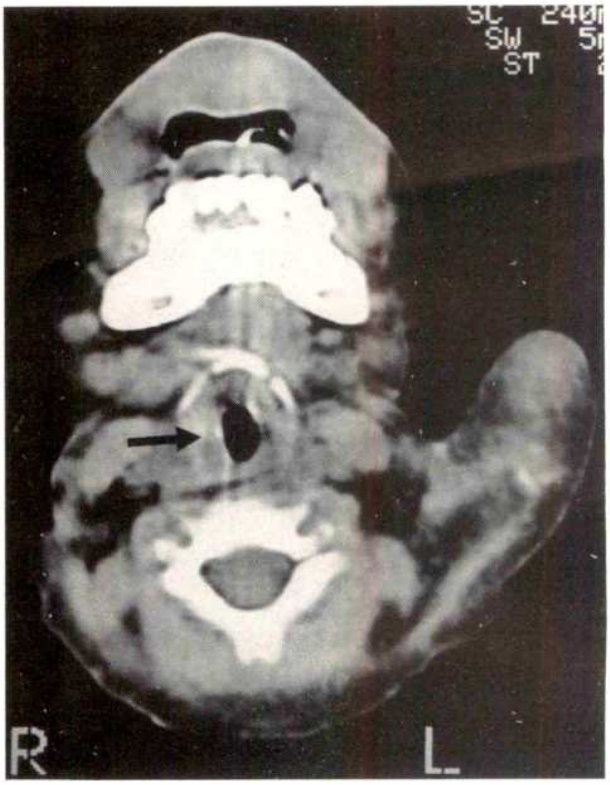


Figure 3 Computed tomography of the neck demonstrating deformation of the right lateral wall of the trachea caused by a hyaline deposit which is marked by an arrow.

PATIENT NO. 2

The younger sister presented for anaesthesia at 2 yr of age for surgical removal of lesions around the mouth. Although she had obvious facial evidence of hyaline deposits she had reasonable mouth opening. A potentially difficult intubation was anticipated as there was no indication of whether or not there might be deposits in and around the pharynx and larynx. Anaesthesia was induced with oxygen and halothane, and laryngoscopy was performed under deep inhalation anaesthesia. The lower jaw was stiff and heavily infiltrated. A straight blade enabled a view of the arytenoids but not the cords. The pharynx appeared normal. A size 3.0-mm oral tracheal tube was passed easily. Fibreoptic review of her nasal passages revealed no abnormality and a 3.0-mm nasal tracheal tube was passed while the oral tracheal tube was removed, so facilitating surgical access.

Discussion

A variety of names have been given to JHF which was first described by Murray in 1873 as "peculiar cases of molluscum fibrosum" [1]. Other names include puretic syndrome, disseminated painful fibromatosis and fibromatosis hyalinica multiplex juvenilis [2]. Infantile systemic hyalinosis is a similar condition but has an earlier onset [3].

JHF is a rare autosomal recessive disorder with variable penetrance. One-third of affected children are siblings and are often born to consanguineous marriages [2]. Clinical features develop in the first few years of life and include: multiple large slow growing cutaneous nodules on the head and neck, which involve the lips and are also found elsewhere on the body, joint contractures, gingival hypertrophy and osteolytic lesions [4–6]. Intellect is often normal [2]. Infiltration of areas such as around the mandible have, as in the two children described here, led to hard unyielding tissues with limited mouth opening. Histologically the lesions consist of an eosinophilic hyaline matrix surrounding well differentiated fibroblasts [4,5]. Previously described postmortem findings in the related disease infantile systemic hyalinosis include hyaline deposits in the skin, trachea, throughout the gastrointestinal tract, the heart, lungs, skeletal muscle, thyroid and adrenal glands [7]. Death, which occurs in the first few decades of life, may be caused by infection and there is predisposition to staphylococcal infection of skin lesions [2,3].

There have been two previous reports of anaesthetic management of JHF. Sugahara and colleagues [8] reported a 6-yr-old with JHF whose trachea was intubated successfully. Vaughn and colleagues [9] reported a 13-month-old child with JHF whose trachea was intubated with the aid of a guide wire passed through the suction port of a fibreoptic bronchoscope. Subsequent laryngoscopy revealed the epiglottis and posterior arytenoids; however, difficulty was noted in seeing the vocal cords.

Our case reports illustrate not only the airway difficulties that may be encountered with this disease, but also that as the disease progresses these are likely to become more difficult in subsequent anaesthetics. This is also the case in other diseases which are characterized by accumulation of abnormal material in the tissues. These diseases include the mucopolysaccharidoses such as Hurler's syndrome [10].

Preoperative assessment of our patients included a search for any co-existing disease but systemic manifestations resulting from hyaline deposits in organs such as the heart, lung and kidney were not present. A computed tomography scan of the pharynx was found to be useful in predicting a difficult airway.

A variety of techniques were used in the anaesthetics reported here, both as the elder sister's disease developed and as experience was gained in anaesthetic management of JHF. In all instances gaseous induction was used as it was considered the safest method to achieve induction while the airway was unsecured.

For the elder sister's first anaesthetic, suxamethonium was used for intubation because its rapid onset allowed the airway to be secured quickly. Its rapid offset would have been useful if neither intubating nor ventilating the patient's lungs with a face mask had proved possible during paralysis. However, it was not found to be necessary to use suxamethonium in any subsequent anaesthetic. Atracurium and positive pressure ventilation were used to avoid hypoventilation. Atracurium was used also in subsequent anaesthetics for the same reason. The one exception was the elder sister's second anaesthetic. In this anaesthetic laryngoscopy was attempted to assess the difficulty of intubation. When laryngoscopy proved impossible a laryngeal mask was used with spontaneous ventilation because the surgical procedure planned was short (approximately 20 min) and did not involve the mouth or face. Spontaneous ventilation was adequate for this period of time.

For the elder sister's third and fourth anaesthetics it was planned to use an intubating fibreoptic bronchoscope from the outset; laryngoscopy in the previous anaesthetic had proved impossible and use of a laryngeal mask was precluded because surgery on the mouth was planned. Under these circumstances the fibreoptic bronchoscope, used while a nasal airway allowed spontaneous ventilation, was found to be invaluable for intubation. For the younger sister's anaesthetic, intubation using laryngoscopy was achieved although the fibreoptic bronchoscope was still used to examine the airway.

Although the fibreoptic intubating bronchoscope was useful to view the airway and to secure it by facilitating intubation, there are limitations to its use. With young children, such as our patients, it is not practical to use it for an awake intubation because of the distress caused. It cannot be used for railroading a tracheal tube into the trachea if the internal diameter of the tracheal tube required is less than the diameter of the bronchoscope available, although using a guide wire passed down the suction port is an option [9]. In addition, the fibreoptic bronchoscope needs to be used by an anaesthetist experienced in its use.

Alternatives to using a fibreoptic brochoscope would have included blind nasal intubation and a bougie inserted down a laryngeal mask. However, blind nasal intubation may cause bleeding, especially in an abnormal airway, while intubating using a fibreoptic brochoscope caused no identifiable haemorrhage in the cases described here. Although no attempt was made to pass a laryngeal mask in the elder sister's last two anaesthetics, it is likely, in view of the findings with the fibreoptic bronchoscope, that a laryngeal mask would have been impossible to insert because of infiltrations in the airway.

Postoperative care was uneventful in the cases described and pain was controlled with mild analgesics. However, there is probably an increased risk of postoperative airway obstruction in patients with JHF and this may be enhanced if postoperative analgesia is required.

In conclusion, JHF, in common with other diseases associated with accumulation of abnormal material in the soft tissues, may cause increasingly severe airway problems with age. Anticipating and preparing for a difficult airway is probably more important than using any particular anaesthetic technique. However, it is recommended that the facilities for fibreoptic intubation and an experienced paediatric anaesthetist are present for all such cases.

References

1. Murray J. On three peculiar cases of molluscum fibrosum in children. *Medico-Chirurgical Transactions* 1873; 38: 235–253.
2. Bedford CD, Sills JA, Sommelet-Olive D, Boman F,

Beltramo F, Cornu G. Juvenile hyaline fibromatosis: a report of two severe cases. *Journal of Pediatrics* 1991; **119**: 404–410.

3. Glover MT, Lake BD, Atherton DJ. Infantile systemic hyalinosis: newly recognized disorder of collagen? *Pediatrics* 1991; **87**: 228–234.
4. Fayad MN, Yacoub A, Salman S, Khuder A, DerKaloustain VM. Juvenile hyaline fibromatosis: two new cases and a review of the literature. *American Journal of Medical Genetics* 1987; **26**: 123–131.
5. Remberger K, Krieg T, Lunze D, Weinmann H, Hubner G. Fibromatosis hyalinica multiplex (juvenile hyaline fibromatosis). *Cancer* 1985; **56**: 614–624.
6. Aldred M, Crawford P. Juvenile hyaline fibromatosis. *Oral Surgery, Oral Medicine, Oral Pathology* 1987; **63**: 71–77.
7. Landing BH, Nadorra R. Infantile systemic hyalinosis: report of four cases of a disease, fatal in infancy, apparently different from juvenile systemic hyalinosis. *Pediatric Pathology* 1986; **6**: 55–79.
8. Sugahara S, Ikezaki W, Abe K, Ogawa R. Anaesthetic management of a patient with juvenile hyaline fibromatosis: a case report. *Masui (Japanese Journal of Anesthesiology)* 1993; **42**: 1853–1855.
9. Vaughn GC, Kaplan RF, Tieche S, Downs JB. Juvenile hyaline fibromatosis: anesthetic management. *Anesthesiology* 1990; **72**: 201–203.
10. Belani KG, Krivit W, Carpenter BL, Braunlin E, Buckley JJ, Liao JC, Floyd T, Leonard AS, Summers CG, Levine S, Whitley CB. Children with mucopolysaccharidosis: perioperative care, morbidity, mortality, and new findings. *Journal of Pediatric Surgery* 1993; **28**: 403–410.

British Journal of Anaesthesia 1996; 76: 167–172

CORRESPONDENCE

Visceral pain during Caesarean section

Sir,—In their article on visceral pain during Caesarean section, Hirabayashi and colleagues [1] stated that "The spread of analgesia in all patients was almost comparable". However, although the upper limit of spread of spinal amethocaine was measured, no attempt was made to define the lower limit of spread. Exteriorization of the uterus may lead to traction on the pelvic viscera, and pain in this region can be conveyed via the pelvic splanchnic nerves (S2, 3, 4 nerve roots) [2]. A more extensive block in the sacral nerve roots, when using higher doses of spinal amethocaine, is a possible explanation for the differences in quality of intraoperative conditions found in their study.

When presenting their data on the maximum spread of analgesia, the authors quoted a range for the upper level of the block which included non-integer values. I fail to see how they can be so accurate, especially when the dermatomal nerve supply varies between subjects and, in fact, the dermatomal chart differs immensely in description among medical books [2, 3].

M. C. Fairfield
Department of Anaesthesia
Leicester Royal Infirmary
Leicester

1. Hirabayashi Y, Saitoh K, Fukuda H, Shimizu R. Visceral pain during Caesarean section: effect of varying dose of spinal amethocaine. *British Journal of Anaesthesia* 1995; 75: 266–268.
2. Snell RS. *Clinical Anatomy for Medical Students*, 2nd Edn. Boston: Little, Brown and Company, 1981.
3. Kumar PJ, Clark ML. *Clinical Medicine*, 2nd Edn. London: Baillière Tindall, 1990.

Sir,—We took no account of the lower limit of spread of spinal amethocaine and our conclusion was indeed derived from the data on the upper limit of analgesia. Although we had no opportunity to examine if the second, third and fourth sacral nerves were blocked during operation, none of our parturients had any sensation in the perineum during and immediately after operation, indicating that these sacral nerves were totally blocked. In contrast with extradural anaesthesia, spinal amethocaine injected at the midlumbar region usually blocks every sacral nerve. From this, we can surmise that there were no differences in the extent of block of the sacral nerves in the parturients.

Visceral pain may be transmitted via pathways as high as the coeliac plexus [1]. The coeliac plexus receives its primary innervation from the greater, lesser and least splanchnic nerves, which arise from T5 to T12 [2]. Hyperbaric anaesthetic solutions, migrating cephalad, pool in the thoracic hollow [3]. A more potent block in this region, when using higher doses of spinal amethocaine, may be a possible reason for the differences in the incidence of visceral pain found in our study.

In our article, data on maximum spread of analgesia were presented as median with range, because data on dermatomal spread are non-parametric. We assessed the spread of analgesia in the left and right sides of the body according to a dermatomal chart given in a standard textbook of neural block [4]. We believe that this female dermatomal chart is one of the most reliable for obstetric and gynaecological patients. If the analgesic levels obtained in both sides differed, the average value was used for analysis, and therefore non-integer values were provided.

Y. Hirabayashi
K. Saitoh
H. Fukuda
R. Shimizu
Department of Anaesthesiology
Jichi Medical School
Tochigi, Japan

1. Brown DL. Spinal, epidural, and caudal anesthesia: Anatomy, physiology, and technique. In: Chestnut DH, ed. *Obstetric Anesthesia. Principles and Practice.* St Louis: Mosby, 1994; 181–201.
2. Brown DL. *Atlas of Regional Anesthesia.* Philadelphia: WB Saunders Company, 1992; 247.
3. Kitahara T, Kuri S, Yoshida J. The spread of drugs for spinal anesthesia. *Anesthesiology* 1965; 17: 205–208.
4. Cousins MJ, Bridenbaugh PO. *Neural Blockade in Clinical Anesthesia and Management of Pain*, 2nd Edn. Philadelphia: JB Lippincott, 1988; 344.

Cannabis as a medicine

Sir,—We read with great interest the editorial by Doyle and Spence [1]. This was a step in the right direction and provides a concise presentation of the more recent research and concepts on the therapeutic potential of *Cannabis sativa.*

The Departments of Pharmacology and Ophthalmology of the University of the West Indies at the Mona Campus in Kingston, Jamaica have performed extensive research with *Cannabis sativa*, focusing on its possible therapeutic potential. Of course we would not advocate smoking cannabis as this could lead to some of the adverse effects described [1]. On the other hand, with regard to the gestational effects, in a long-term study in Jamaica by Dr Milaine Dreher from the University of Massachusetts and Dr Ronald Lampart in Morant Bay, Jamaica, no unusual fetal effects or growth retardation were observed. This study included mothers in early pregnancy, smoking *Cannabis sativa* through pregnancy and delivery, and their offspring were followed-up for 5 years.

Furthermore, with regard to mortality, intensive search of the literature has, to our knowledge, reported no deaths from cannabis *per se*, although the CNS effects may result in "fatalities" of one type or another.

In support of cannabis as a medicine, West and Lockhart [2, 3] from the University of the West Indies have developed an ethical preparation, an eye drop for topical administration of *Cannabis sativa*. This preparation has been marketed since 1987 and several thousand 5-cc phials have been used in some parts of the world in the management of glaucoma, particularly in the Caribbean region and some parts of North America. The drug is marketed under the tradename Canasol eye drops. In Jamaica it is manufactured by Ampec Chemicals Limited and marketed by Medigrace Limited, Kingston. Canasol is comparable with timolol maleate and is compatible with the commonly used anti-glaucoma medication. The use of Canasol eye drops has also been reported by Gutierrez and Gutierrez [4].

We agree entirely that further research is required into the use of *Cannabis sativa* or its derivatives as an analgesic and antiemetic in the postoperative period and also in the hospice setting. Even if it were to be shown that cannabis is no more useful than existing drugs, it remains a significantly cheaper and more accessible alternative in those developing countries where the newer preparations marketed by the large multinational pharmaceutical companies are unaffordable and unavailable to the general population.

M. E. West
Department of Pharmacology
J. Homi
Department of Anaesthetics and
Intensive Care
University of the West Indies
Kingston, Jamaica

1. Doyle E, Spence AA. Cannabis as a medicine. *British Journal of Anaesthesia* 1995; 74: 359–361.
2. West ME, Lockhart AB. The treatment of glaucoma using a non-psychoactive preparation from *Cannabis sativa. West Indian Medical Journal* 1978; 27: 16–25.
3. West ME, Lockhart AB. The synergistic effect of Canasol and timolol maleate eye drops in glaucoma patients. *World Conference on Clinical Pharmacology and Therapeutics* (Paper No. 0100). London, 1980.
4. Gutierrez AM, Gutierrez DL. Ocular hypertension treatment with Cannabis sativa 1990; Paper presented at the Annual Congress of Ophthalmology, Cali, Colombia, August 1995.

Naproxen after day-case laparoscopic sterilization

Sir,—The recent article by Dunn, Clark and Jones [1] on the analgesic efficacy of a single preoperative dose of naproxen in patients undergoing day-case laparoscopic tubal ligation yet again demonstrates that pain after this procedure can rarely be treated by non-steroidal anti-inflammatory drugs (NSAID) alone. There is no doubt that pain is a very significant factor in the morbidity after laparoscopic tubal ligation [2–4]. On repeated occasions, previously published work has shown NSAID to be only partially successful in treating this pain when administered as the sole analgesic [2, 5–8].

Although there is evidence that prostaglandins mediate the pain associated with tubal ligation [9], it seems, as observed by Dunn, Clark and Jones, that this particular pain is multimodal in origin with subphrenic and shoulder tip pain originating from the persistence of irritating intraperitoneal insufflating gas [10] and cephalad tracking of blood or free fluid from the operative site via the paracolic gutters [11], and pelvic pain originating from the use of rings, clips or diathermy to occlude or interrupt the Fallopian tubes [10]. It is therefore not surprising that administration of NSAID as the lone therapeutic manoeuvre to treat this pain has proved unsuccessful. It is surely more sensible to consider NSAID as an integral component of "balanced analgesia" under such circumstances as opposed to the sole analgesic agent. It is probable that there is a proportion of patients undergoing laparoscopic tubal ligation whose postoperative pain will necessitate administration of opioid analgesia and who may, indeed, go on to require overnight hospital admission.

P. I. Williams
Department of Anaesthesia
Alder Hey Children's Hospital
Liverpool

1. Dunn TJ, Clark VA, Jones G. Preoperative oral naproxen for pain relief after day-case laparoscopic sterilization. *British Journal of Anaesthesia* 1995; 75: 12–14.
2. Edwards ND, Barclay K, Catling SJ, Martin DG, Morgan RH. Day case laparoscopy: a survey of postoperative pain and an assessment of the value of diclofenac. *Anaesthesia* 1991; 46: 1077–1080.
3. Davis A, Millar JM. Postoperative pain: a comparison of laparoscopic sterilisation and diagnostic laparoscopy. *Anaesthesia* 1988; 43: 796–797.
4. Fraser RA, Hotz SB, Hurtig JB, Hodges SN, Moher D. The prevalence of pain after day-care tubal ligation surgery. *Pain* 1989; 39: 189–201.
5. MacLennan AH, Rodrigues LV, Krutli DR, Klomp A. Postoperative discomfort after ring or clip tubal ligation—is there any difference and do indomethacin suppositories help? *Contraception* 1990; 42: 309–313.
6. Crocker S, Paech M. Preoperative rectal indomethacin for analgesia after laparoscopic sterilisation. *Anaesthesia and Intensive Care* 1992; 20: 337–340.
7. Shapiro MH, Duffy BL. Intramuscular ketorolac for postoperative analgesia following laparoscopic sterilisation. *Anaesthesia and Intensive Care* 1994; 22: 22–24.
8. Higgins MS, Givogre JL, Marco AP, Blumenthal PD, Furman WR. Recovery from outpatient laparoscopic tubal ligation is not improved by preoperative administration of ketorolac or ibuprofen. *Anesthesia and Analgesia* 1994; 79: 274–280.
9. Brodie BL, Casper RF. Prostaglandins mediate postoperative pain in Falope ring sterilisation. *American Journal of Obstetrics and Gynecology* 1985; 151: 175–177.
10. Dobbs FF, Kumar V, Alexander JI, Hull MGR. Pain after laparoscopy related to posture and ring versus clip sterilisation. *British Journal of Obstetrics and Gynaecology* 1987; 94: 262–266.
11. Boheimer NO, Thomas JS, Bowen-Simpkins P. Pain after laparoscopy. *Anaesthesia* 1990; 45: 253–254.

Sir,—As Dr Williams correctly points out, it would be inappropriate to treat the pain of laparoscopic tubal ligation with NSAID alone because of the multimodal nature of the pain. We therefore added NSAID to our normal practice of giving i.v. diamorphine during operation to extend the number of pain mechanisms being targeted. Before this study our patients commonly required additional diamorphine for postoperative pain relief, with its increased risks of nausea, vomiting and sedation, and subsequent increased likelihood of overnight stay. Our bimodal approach, using diamorphine and naproxen, decreased the need for extra postoperative diamorphine (naproxen group 21:37 = 54%; placebo group 27:35 = 77%). However, our conclusion was that a trimodal approach was required, which included a third component, local anaesthesia.

T. J. Dunn
V. A. Clark
G. Jones
Department of Anaesthesia
Eastern General Hospital
Edinburgh

Systolic pressure variation—a way to recognize dynamic hyperinflation

Sir,—I read with interest the article by Myles, Madder and Morgan [1], the similar case presented by Mercer [2], and the reply of Myles [3], concerning cardiac arrest after unrecognized dynamic hyperinflation. The potential fatality of dynamic hyperinflation often stems from lack of recognition. I would therefore suggest that analysing the respiratory variations in the arterial pressure waveform may serve as an early warning sign of such hyperinflation. The arterial pressure waveform responds normally in a biphasic manner to a mechanical breath [4]. This response starts with an early increase in systolic pressure, termed by us delta up (dUp), which denotes transient augmentation of left ventricular (LV) stroke output caused mainly by squeezing down of pulmonary blood into the LV. The dUp is followed normally by a decrease in systolic pressure, termed delta down (dDown), which is caused by the inspiratory decrease in venous return. The difference between maximal and minimal systolic pressures during one mechanical breath is termed the systolic pressure variation (SPV) [4]. SPV and dDown (the difference between systolic pressure during a short apnoea and the minimal systolic value) are sensitive indicators of reduction in preload [4–7]. A build up of positive intrathoracic pressure during dynamic hyperinflation reduces venous return and effective preload, and therefore leads to exaggerated depressions of LV output (and arterial pressure) with each mechanical breath.

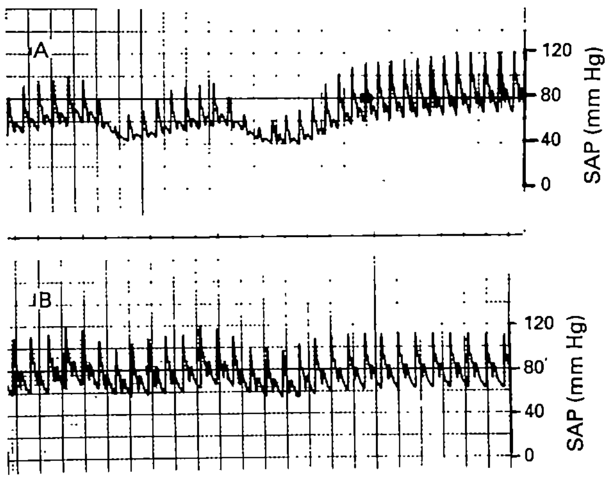


Figure 1 Systolic arterial pressure (SAP) waveform indicating hyperinflation (A), caused by the tip of the tracheal tube abutting on the tracheal wall. Withdrawing the tracheal tube resulted in lung deflation and a normal waveform variation (B).

Such a case is described in figure 1, where hyperinflation (A) was caused by the tip of the tracheal tube abutting on the tracheal wall and causing a one-way valve mechanism. Excessive airway pressure caused the appearance of pronounced SPV with every breath. A short apnoea caused systolic pressure to increase significantly and to be characteristically higher than peak systolic pressure during mechanical ventilation. Withdrawing the tracheal tube resulted in lung deflation and a normal arterial pressure waveform variation (B).

Hence, the appearance of excessive SPV and dDown should indicate frank hypovolaemia or any other mechanism that reduces preload, such as dynamic hyperinflation. The significant increase in systolic pressure during introduction of a short apnoea is indicative of such hyperinflation. In the absence of a direct arterial pressure trace, variations in the plethysmographic signal of the pulse oximeter may reflect the same phenomenon.

A. PEREL
E. SEGAL
Department of Anaesthesia
and Intensive Care
Sheba Medical Center
Tel Hashomer, Israel

1. Myles PS, Madder H, Morgan EB. Intraoperative cardiac arrest after unrecognized dynamic hyperinflation. *British Journal of Anaesthesia* 1995; 74: 340–342.
2. Mercer M. Cardiac arrest after unrecognized dynamic inflation. *British Journal of Anaesthesia* 1995; **75**: 252.
3. Myles PS. Cardiac arrest after unrecognized dynamic inflation. *British Journal of Anaesthesia* 1995; **75**: 252.
4. Perel A, Pizov R, Cotev S. The systolic pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. *Anesthesiology* 1987; **67**: 498–502.
5. Pizov R, Ya'ari Y, Perel A. Systolic pressure variation is greater during hemorrhage than during sodium nitroprusside induced hypotension in ventilated dogs. *Anesthesia and Analgesia* 1988; **67**: 170–174.
6. Coriat P, Vrillon M, Perel A. A comparison of systolic blood pressure variations and echocardiographic estimates of end-diastolic left ventricular size in patients after aortic surgery. *Anesthesia and Analgesia* 1994; **78**: 46–53.
7. Rooke GA, Schwid HA, Shapira Y. The effect of graded hemorrhage and intravascular volume replacement on systolic pressure variation in humans during mechanical and spontaneous ventilation. *Anesthesia and Analgesia* 1995; **80**: 925–932.

Sir,—I appreciate the interesting comments of Perel and Segal who highlight the possible detection of dynamic hyperinflation (DHI) by changes in the arterial waveform with respiratory excursions. Pulse oximetry has also recently been suggested [1], although electronic adjustment of some pulse oximeters makes direct arterial pressure measurement more reliable [2]. Nevertheless, as suggested by Perel and Segal, there are other causes of exaggerated systolic pressure variation (vasodilatation, hypovolaemia) which often coexist after induction of anaesthesia and commencement of positive pressure ventilation. This is when DHI usually manifests. I therefore strongly recommend that DHI is best diagnosed with an apnoeic period, which not only accurately diagnoses the problem, but can quantify the extent of DHI (by measuring the expired gas volume during this period) while offering expeditious treatment. Such an apnoeic period should include insufflation with 100% oxygen and may require more than 90 s for a response [3].

Incidentally, because of the mechanism outlined by Perel and Segal, an apnoeic period may also transiently relieve some of the adverse haemodynamic effects of intravascular volume depletion in patients with obstructive lung disease.

P. S. MYLES
Alfred Hospital
Melbourne
Australia

1. Conacher ID, McMahon CC. Pathognomonic pulse oximetry paradox. *Lancet* 1995; **346**: 448.
2. Myles PS, Ryder I. Pulse oximetry. *Lancet* 1995; **346**: 850.
3. Myles PS, Weeks AM. Alpha 1-antitrypsin deficiency: circulatory arrest following induction of anaesthesia. *Anaesthesia and Intensive Care* 1992; **20**: 358–362.

Intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia

Sir,—I read with interest the recent report by Robbins, Fernando and Lim on accidental intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia for Caesarean section [1]. Clearly, it is important to report on complications associated with new anaesthetic techniques, such as combined spinal–extradural anaesthesia. I also fully concur with the authors' conclusion that an appropriate test dose be administered through an extradural catheter to exclude intrathecal placement.

However, I believe that the phenomenon of submission bias and publication bias be considered in the interpretation of this report. It is well known that intrathecal migration of an extradural catheter can occur at any time, even without obvious dural puncture. Had such an event occurred during routine extradural anaesthesia (i.e. without combined spinal–extradural anaesthesia), it is unlikely that such a case would have been submitted, and if submitted, it would be unlikely to be accepted for publication. To the authors of this report, and to any others who claim that intrathecal catheter migration is a specific risk of combined spinal–extradural anaesthesia, I challenge that the onus is upon you to prove that this event occurs with any greater frequency during combined spinal–extradural anaesthesia than during routine extradural anaesthesia. In fact, the available evidence in the literature, including large clinical studies [2–4] and laboratory investigations [5], would support the claim that the incidence of intrathecal catheter migration is ***not increased*** when combined spinal–extradural anaesthesia is used. Even outspoken opponents [6] of the needle-through-needle combined spinal–extradural anaesthesia technique have not provided any evidence that this approach increases the risk of intrathecal catheter migration, nor is there any evidence that alternative needle designs decrease the incidence of this occurrence.

When new techniques, such as combined spinal–extradural anaesthesia, are used it is important that complications are documented. However, old, well-known, but infrequent complications of extradural anaesthesia, such as catheter migration, should not be ascribed improperly to new techniques on the basis of isolated case reports. Unfortunately, much of the dogma by which we practise is based on isolated case reports, when large-scale studies would seem to indicate otherwise.

W. CAMANN
Department of Anesthesia
Brigham and Women's Hospital
Boston, MA, USA

1. Robbins PM, Fernando R, Lim GH. Accidental intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia for Caesarean section. *British Journal of Anaesthesia* 1995; **75**: 355–357.
2. Morgan B, Kadim MY. Mobile regional anaesthesia in labour. *British Journal of Obstetrics and Gynaecology* 1994; **101**: 839–841.
3. Collis RE, Davies DWL, Aveling W. Randomized comparison of combined spinal–epidural and standard epidural analgesia in labour. *Lancet* 1995; **345**: 1413–1416.
4. Norris MC, Grieco WM, Borkowski M. Complications of labor analgesia: Epidural versus combined spinal–epidural techniques. *Anesthesia and Analgesia* 1994; **79**: 529–537.
5. Holmstrom B, Rawal N, Axelsson K, Nydahl PA. Risk of catheter migration during combined spinal epidural block: Percutaneous epiduroscopy study. *Anesthesia and Analgesia* 1995; **80**: 747–753.
6. Eldor J, Guedj P. Aseptic meningitis due to metallic particles in the needle-through-needle technique. *Regional Anesthesia* 1995; **20**: 360.

Sir,—In a recent case report, Robbins, Fernando and Lim described the presumptive placement of an extradural catheter through the hole made by a 26-gauge Whitacre needle [1].

The authors are correct in stating that only diagnostic studies (MRI or x-ray contrast) can definitively confirm that diagnosis. It is not impossible that bupivacaine 12.5 mg could provide analgesia and increased motor block even if it were injected into the extradural space. We have now seen several cases where CSF could be aspirated from an extradural catheter after a spinal block was made with a 24- or 26-gauge pencil point needle passed through the extradural needle before catheter placement. In one instance, we were so concerned that the catheter was subarachnoid that it was removed and a new catheter was placed one interspace cephalad, at which time some CSF appeared in the hub of the extradural needle (*not* a gush!) and a small amount of CSF could be aspirated through the catheter after it was placed.

After careful evaluation, this catheter was treated as if it were in the extradural space and a continuous infusion of 0.0625% bupivacaine and sufentanil was started. Based on spread and density of block, the catheter appeared to be in the extradural space rather than subarachnoid. This leads us to believe that a small percentage of patients may develop a clinically detectable and immediate CSF leak even when subarachnoid puncture is made with a small gauge pencil point needle. Interestingly, none of our patients developed a clinically detectable post-lumbar puncture headache.

As an aside, we also wonder whether Caesarean should be spelled with a capital C, as it was in this case report. We believe the word derives from the Latin verb for cut and is, in fact, often spelled cesarean, at least on this side of the Atlantic.

J. S. Lee
T. Abboud
Department of Anesthesiology
University of Southern California
Los Angeles, CA, USA

1. Robbins PM, Fernando R, Lim GH. Accidental intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia for Caesarean section. *British Journal of Anaesthesia* 1995; 75: 355–357.

Sir,—Thank you for the opportunity to reply to the letters of Dr Camann, and Dr Lee and Professor Abboud regarding our case report [1].

Camann suggests that the risk of migration of an extradural catheter is no greater with combined spinal–extradural anaesthesia than with extradural anaesthesia alone. We have two points to raise on the matter. First, we claimed that the catheter was placed intrathecally and did not migrate to this position. Second, we believe that an extradural catheter will not migrate through intact dura at any time. Holmstrom and colleagues [2] make the point that it is unlikely that an extradural catheter enters a hole made by a spinal needle. By implication such an occurrence is even more unlikely to occur if there is *no* hole made in the dura. We feel that many of these reports may have occurred when the dura was punctured accidentally at some moment by the extradural needle. Even small movements of the needle might cause unintentional damage [3].

We are also not implying that extradural catheter migration is increased with the combined spinal–extradural technique, and agree with Dr Camann that isolated case reports should not prevent its acceptance into practice. However, we do feel that this safe technique is improved by the knowledge that intrathecal catheter placement could occur, and the obvious complications of such placement could be avoided by aspiration and a test dose. In our obstetric unit not only are all elective Caesarean sections performed using combined spinal–extradural anaesthesia, but 75% of all regional blocks for labour analgesia are initiated using the same technique.

Dr Lee and Professor Abboud state that bupivacaine 12.5 mg could have caused the increase in motor and sensory block that we observed after operation, even if it were administered extradurally. We cannot agree with this comment. We gave a 12.5-mg (2.5 ml) injection which, after allowing for the deadspace of the catheter and filter, delivered 7.5 mg (1.5 ml) to the patient. Fink [4] makes the point that it is the length of nerve exposed to local anaesthetic solution that is important. Therefore, it is unlikely that a 12.5-mg (2.5 ml) bolus, let alone a 7.5-mg (1.5 ml) bolus, will have a significant effect if administered into the extradural space, even if sufficient time was allowed.

We agree that some CSF may be seen in the catheter or extradural needle after the spinal needle is removed. This is caused by pressure (especially if the patient is in the sitting position during the combined spinal–extradural anaesthesia) causing CSF to leak out of the spinal needle hole and is not a result of dural puncture with the extradural needle. Based on our continuous positive aspiration and on the speed and density of the block with bupivacaine 7.5 mg, we believe that our catheter was subarachnoid.

Caesarean was spelt with a capital C by the editors of the *British Journal of Anaesthesia*. We have found numerous derivations, including the mechanism of Caesar's birth, and from *Lex Caesarea* (the law of removing a fetus from a dead mother before burying her). Also, the Latin to cut is caedere (with ae) or scalpere. Caesarean may be spelt cesarean in the USA together with anesthesia, pediatrics, labor, and color, but on our side of the Atlantic we believe that we are correct.

P. M. Robbins
R. Fernando
Royal Free Hospital
London
G. Lim
Whittington Hospital
London

1. Robbins PM, Fernando R, Lim GH. Accidental intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia for Caesarean section. *British Journal of Anaesthesia* 1995; 75: 355–357.
2. Holmstrom B, Rawal N, Axelsson K, Nydahl PA. Risk of catheter migration during combined spinal epidural block: Percutaneous epiduroscopic study. *Anesthesia and Analgesia* 1995; **80**: 747–753.
3. Meiklejohn BH. The effect of rotation of an epidural needle. *Anaesthesia* 1987; **42**: 1180–1182.
4. Fink BR. Mechanisms of differential axial blockade in epidural and subarachnoid anesthesia. *Anesthesiology* 1989; **711**: 851–858.

Editor's Note

We also believe that we are correct in ascribing the derivation of Caesarean to the famous Roman gentleman.

Editor

RAE tube obstruction during tonsil dissection

Sir,—A 41-kg, 9-yr-old boy was admitted for adenotonsillectomy after recurrent attacks of tonsillitis and frequent bouts of snoring. Penicillin allergy was the only other history of note. Premedication included oral diazepam 6 mg, atropine 0.6 mg and topical EMLA.

A spontaneous breathing technique was planned using incremental injected isoflurane into a low-flow circle system. The trachea was intubated with an RAE 6.5-mm, preformed uncuffed orotracheal tube, and the patient attached to a Datex monitor for full non-invasive cardiorespiratory monitoring. The ENT surgeon inserted a Boyle–Davis gag using an 8.8-cm tongue plate, and examination revealed bilateral hypertrophic tonsils, but absence of enlarged adenoid tissue, and therefore adenoidectomy was unnecessary. Initial surgery and anaesthesia were uneventful but prolonged because of difficult dissection and haemostatic control of the left inferior tonsillar pole. To facilitate easier access and better haemostatic control, the tongue plate used initially was removed and a 10-cm blade inserted. After a few minutes, several events occurred simultaneously; oximetric saturation decreased rapidly, the reservoir bag became partially collapsed, while the surgeon noticed that the RAE tube had herniated through the gap of the tongue plate. Oxygen 100% was administered and a diagnosis of partial tracheal tube obstructed was made. Examination demonstrated that at the point of maximum convexity, the RAE tube had herniated through the gap of the blade, had become kinked and produced flaring of the edges which prevented removal of the tube, but had not caused complete lumen obstruction (fig. 1). Despite several attempts to extricate the RAE tube, it remained jammed in the blade. Therefore, although pulse oximetry returned to normal and tonsillar haemorrhage remained a problem, both RAE tube and gag were removed after pharyngeal suction and cricoid pressure were applied. Re-intubation was performed successfully with the same sized RAE tube, but using an 8.8-cm tongue plate. Subsequent surgery and anaesthesia proved uneventful, and the patient made an uncomplicated postoperative recovery.

The literature describes two reports; Shirley, Kulkarni and Frost [1], and Sen and Gupta [2] both communicated an episode of tube herniation through the Doughty blade during a similar procedure and noted remarkable difficulty in separating the RAE tube from the tongue plate. Contributory factors to tube herniation may have included: the use of a 6.5-mm RAE tube with a 10-cm blade, prolonged surgery causing tube softening and frequent repositioning of the Boyle–Davis gag because of surgical technical difficulties. Prevention of such herniation may include

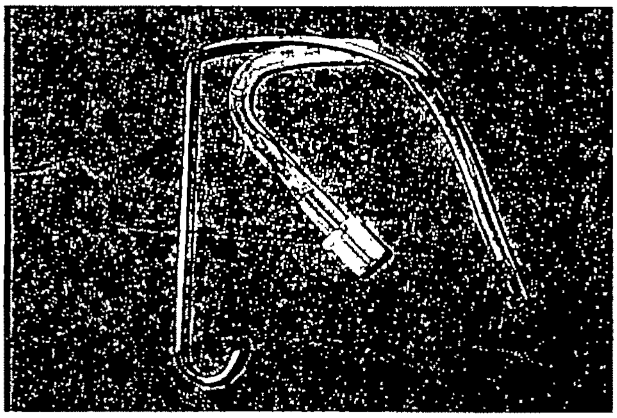


Figure 1 The RAE tube. At the point of maximum convexity, the RAE tube herniated through the gap of the blade, became kinked and produced flaring of the edges.

the use of a more rigid or reinforced tracheal tube [1], a bridge bar, as suggested by Oliver and Rao [3], or the use of a smaller Boyle–Davis gag, as suggested by Baigent and Dunn [4]. This case report not only highlights the need for vigilance during routine elective surgery, but also the value of surgical opinion and communication in helping to alert the anaesthetist to problems during upper airway surgery.

D. GRAHAM
H. S. KADDOUR
Department of Anaesthesia
Leeds General Infirmary
Leeds

1. Shirley PJ, Kulkarni V, Frost N. A problem with the Boyle–Davis gag following difficult intubation. *Anaesthesia* 1994; **49**: 551–552.
2. Sen K, Gupta B. Herniation of RAE tube through split Boyle Davis gag. *Anaesthesia and Intensive Care* 1990; **18**: 577–578.
3. Oliver JJ, Rao J. Modification of the Doughty blade for the Boyle–Davis gag. *Anaesthesia* 1994; **49**: 89.
4. Baigent DF, Dunn B. Possible hazards with RAE preformed tracheal tubes. *Anaesthesia* 1984; **39**: 714–715.

Extradural clonidine for postoperative pain relief

Sir,—I read with interest the article by Lee and Rubin [1] which showed that caudal clonidine 2 μg kg^{-1} with 0.25% bupivacaine 1 ml kg^{-1} improved postoperative analgesia in paediatric patients undergoing lower limb orthopaedic surgery compared with caudal 0.25% bupivacaine alone. Although their results are consistent with another recent report [2], I have recently observed better postoperative analgesia using thoracic extradural clonidine with morphine than morphine alone in adults after gastrectomy [3].

In our study the intensity of pain was assessed by a member of staff who was blinded to the treatment, while each patient received i.v. morphine via a patient-controlled analgesia system as supplementary analgesia. Clinical evaluation of pain is possible in both an objective and subjective manner in adults, but that is not always the case in small children. Based on these considerations, I cannot exclude the possibility that intense sedation induced by extradural clonidine (with local anaesthetics) [4] would make estimation of pain intensity impossible. I also believe that some bias is likely to be introduced in the quantitative assessment of analgesia, especially in paediatric patients, if the patients receive analgesics only when the attending staff judges its requirement.

T. NISHIKAWA
Department of Anaesthesiology
Institute of Clinical Medicine
University of Tsukuba
Tsukuba City, Ibaraki, Japan

1. Lee JJ, Rubin AP. Comparison of a bupivacaine–clonidine mixture with plain bupivacaine for caudal analgesia in children. *British Journal of Anaesthesia* 1994; **72**: 258–262.
2. Jamali S, Monin S, Begon C, Dubousset A-M, Ecoffey C. Clonidine in pediatric caudal anesthesia. *Anesthesia and Analgesia* 1994; **78**: 663–666.
3. Anzai Y, Nishikawa T. Thoracic epidural clonidine and morphine for postoperative pain relief. *Canadian Journal of Anaesthesia* 1995; **42**: 292–297.
4. Nishikawa T, Dohi S. Clinical evaluation of clonidine added to lidocaine solution for epidural anesthesia. *Anesthesiology* 1990; **73**: 853–859.

Porphyria, propofol and rats

Sir,—I read with interest the study of Böhrer and colleagues [1] investigating the porphyrinogenicity of propofol in an induced rat model. I was somewhat surprised by aspects of their study design and subsequent attempts to extrapolate their results to the human anaesthetic state.

In a statement in their summary, an acute porphyric attack was described as largely a dose-dependent phenomenon. Yet, in their study, they chose to induce a state of prolonged sedation (the rats were readily rousable), rather than anaesthesia. This would have obvious inferences on blood propofol concentrations and potential porphyrinogenic effect. The reliance on the i.p. route of drug administration, while technically more convenient than the i.v. route, would imply that blood propofol concentrations were less controllable, and may explain why in the pilot study to establish the dose of propofol, they found it difficult to induce anaesthesia without the problems of irregular respiration and hypothermia. In a similar study, Harrison, Moore and Meissner [2] induced anaesthesia by the i.p. route, followed by maintenance by the i.v. route; this would seem to be a better model to parallel anaesthesia.

While successfully demonstrating another *in vivo* model for biochemical assessment of drug porphyrinogenicity, the study fails to recognize the difficulties of extrapolating such data to the human state. Harrison, Moore and Meissner stated that the behaviour of a drug in an animal model to assess porphyrinogenicity was far removed from proof that it was potentially safe or dangerous to a human sufferer with genetic porphyria. It simply serves to show that in that particular animal model, the drug either displays or fails to display properties known to characterize drugs that do precipitate crises in susceptible humans. Drug metabolism differs profoundly between species; even animals so apparently similar as rats and mice show marked variation in the response of their haem biosynthetic pathway to the effects of various drugs. Disler and colleagues [3] placed this type of work in context, by devising a simple classification of drugs to guide clinicians in the assessment of a drug's porphyrinogenicity.

To attempt to extrapolate such data would be to assume a simple relationship between a drug's ability to induce increased levels of porphyrin precursors in an *in vivo* animal model and its ability to induce a clinical attack. This is clearly not the case. The situation is far more complex, as illustrated by Mustajoki and Heinonen [4] who reported several cases where patients with acute porphyria received various porphyrinogenic drugs (including thiopentone) without clinical effect. This has led to the suggestion that sensitivity to a particular drug may depend on whether or not the patient is in the latent or acute phase of the disease, and on other factors, including endocrine and carbohydrate status at the time of administration.

Finally, the suggested caution regarding the use of propofol for total i.v. anaesthesia and cumulative dosing must also be viewed with some degree of scepticism. Apart for the reasons indicated above, I also suggest a closer review of the case reports used as references. Of the 10 cases, the majority received either repeated boluses or propofol infusions. One patient [5] admitted to the ITU because of neurological sequelae from an acute attack of porphyria received propofol at a dose of 150–200 mg h^{-1} for 32 days without adverse biochemical or clinical effects. Where measured, urinary porphyrin precursors in these studies tended to decrease rather than increase.

M. D. TIDMARSH
Department of Anaesthesia
Leicester Royal Infirmary
Leicester

1. Böhrer H, Schmidt H, Martin E, Lux R, Bolsen K, Goerz G. Testing the porphyrinogenicity of propofol in a primed rat model. *British Journal of Anaesthesia* 1995; **75**: 334–338.
2. Harrison GG, Moore MR, Meissner PN. Porphyrinogenicity of etomidate and ketamine as continuous infusions. Screening in the DDC-primed rat model. *British Journal of Anaesthesia* 1985; **57**: 420–423.

3. Disler PB, Blekkenhorst GH, Eales L, Moore MR, Straughan J. Guidelines for drug prescription in patients with the acute porphyrias. *South African Medical Journal* 1982; **61**: 656–660.
4. Mustajoki P, Heinonen J. General anesthesia in "inducible" porphyrias. *Anesthesiology* 1980; **53**: 15–20.
5. Harrison JC, McAuley FT. Propofol for sedation in intensive care in a patient with an acute porphyric attack. *Anaesthesia* 1992; **47**: 355–356.

Sir,—The safety of propofol as an anaesthetic agent in human acute porphyrias is well established clinically. With such rare disorders, it is inevitable that most evidence should have been acquired by favourable single case reports (e.g. references [24–32], cited in reference [1]). A prospective study involving 13 patients represents a major confirmation of its safety [2].

Various models of the porphyrinogenicity of drugs in rats, chick embryo or chick embryo liver systems have been devised as a guide to the safety in porphyria of newly introduced therapeutic agents. Direct extrapolation of the findings to humans is not always possible, although some degree of correlation has been obtained with many agents. Before a new drug which has been shown to be highly porphyrinogenic in such a model system is used in a porphyric subject, there would have to be an overwhelming clinical need, not satisfied by available safe drugs. In a similar way, drugs apparently devoid of porphyrinogenic effects in model systems cannot be assumed to be innocuous to porphyric subjects. The gold standard remains careful human evaluation with facilities for early intervention.

Böhrer and colleagues [1] reported a study testing the porphyrinogenicity of propofol in a primed rat model and concluded that "it is a safe agent in the porphyric patient when given as a single bolus dose. Caution may be necessary, however, when large cumulative doses are administered". The logic of this conclusion is difficult to understand, as are the reasons justifying the work: even if their model had shown propofol to be highly porphyrinogenic (as was the case in the primed chick embryos, which they reject as "too sensitive"), this would not have affected its established clinical use. When an anaesthetist has to make a choice, the precedents available from patients would surely prevail over results obtained with 48, or even 48000 rats.

A. Gorchein
Imperial College of Science, Technology
and Medicine
London

1. Böhrer H, Schmidt H, Martin E, Lux R, Bolsen K, Goerz G. Testing the porphyrinogenicity of propofol in a primed rat model. *British Journal of Anaesthesia* 1995; **75**: 334–338.
2. Meissner PN, Harrison GG, Hift RJ. Propofol as an i.v. anaesthetic induction agent in variegate porphyria. *British Journal of Anaesthesia* 1991; **66**: 60–65.

Sir,—We appreciate Tidmarsh's and Gorchein's comments on our article which was published recently in *British Journal of Anaesthesia*. We agree with both that there is no straightforward extrapolation of laboratory findings to the clinical setting which can be summarized by the simple expression "humans are not rats".

However, it has been known for many decades that laboratory data may be relevant to the clinical situation. Drugs showing toxic effects in animal models may be used with caution in humans. When applied to porphyria, a drug which caused porphyrinogenic effects in the animal model may be used with more reluctance in the patient. Non-clinical assessment of the porphyrinogenicity of drugs has been made in the chick embryo liver cell culture, in the chick embryo *in ovo* and in rats with experimentally induced porphyria. In our study, we have chosen the *in vivo* rat model which may be more relevant to the clinical situation than the other systems mentioned. In Disler's article quoted by Tidmarsh, the authors categorized drugs according to clinical experience and animal experiments; category A is based on human experience reported by three or more authors, B on human experience reported by one or two authors, C on experiments in rats and D on experiments in cell culture or *in ovo*. In our study, we used spontaneously breathing rats to avoid the hepatic effects of 6 h of mechanical ventilation, and at the end of this 6-h period, blood concentrations of propofol and phenobarbitone were measured to ensure significant levels.

In humans, acute hepatic porphyria is a complex disease. It is a pharmacogenetic disorder with variable penetrance, and acute attacks may be precipitated by a multitude of factors, including stress, infection, starvation, hormone changes and drugs. Variable penetrance implies that there is considerable intra- and inter-individual variability in the response to drugs. One porphyric patient may tolerate a continuous drug infusion over 32 days [1], while others may react adversely to doses of 1225 mg [2] or 1300 mg [3] of propofol. Thus when closely reviewing the case reports quoted and other data available, we believe that propofol can be considered safe when give as a single bolus or even as a double-bolus technique. With regard to the variable penetrance of the disease and the unpredictable occurrence of acute attacks, however, we would not use continuous infusions with total doses greater than 1000 mg in our patients. Moreover, for patients in the latent stage of acute hepatic porphyria, it may be better to avoid general anaesthesia and to offer a regional anaesthetic technique [4] in spite of the occurrence of neuropathological lesions.

H. Böhrer
Department of Anaesthesia
University of Heidelberg
Heidelberg, Germany

1. Harrison JC, McAuley FT. Propofol for sedation in intensive care in a patient with an acute porphyric attack. *Anaesthesia* 1992; **47**: 355–356.
2. Bichel T, Joris J, Jacquet N, Lamy M. Total intravenous anaesthesia in South-African genetic porphyria (variegate porphyria). *Acta Anaesthesiologica Belgica* 1993; **44**: 25–29.
3. Elcock D, Norris A. Elevated porphyrins following propofol anaesthesia in acute intermittent porphyria. *Anaesthesia* 1994; **49**: 957–958.
4. Böhrer H, Schmidt H. Regional anesthesia as anesthetic technique of choice in acute hepatic porphyria. *Journal of Clinical Anesthesia* 1992; **4**: 259.

British Journal of Anaesthesia 1996; **76**: 173–174

BOOK REVIEWS

Baillière's Clinical Anaesthesiology: New Pharmacological Vistas. E. J. FINK JR AND B. B. BROWN JR (editors). Published by Baillière Tindall, London. Pp. 212; indexed; illustrated. Price £30.00.

The present volume consists of a dozen chapters on various topics. These vary from the new inhalation agents, sevoflurane and desflurane, to the use of nitric oxide, blood substitutes and calcium channel blockers, in addition to the usual updates on i.v. agents, opioids and neuromuscular blockers. As is usual with a multi-author book, the style and content vary from chapter to chapter but overall the content is clearly presented and is a very useful update on what is happening in the pharmacological world.

The topics related directly to anaesthesia, such as inhalation agents and antiemetics, contain very little new material but do provide an excellent summary of the available information for those involved in examinations or teaching. Unfortunately, the chapter entitled "New intravenous induction agents" contains an excessive amount of historical data, including sections on etomidate, propanidid and ketamine. Although some of the information is related to the effects of optical isomers and newer formulations, less than one-third of the references cover the past 3 years. Similarly, some of the information on propofol was written as "new" when in fact it has been known for well over 5 years. The only "new drug" in this section is eltanolone, a steroid being developed as a potential follow-up to Althesin. The potential advantage of the agent is favourable safety characteristics, although its clinical role remains to be identified.

In contrast, the two chapters on the new opioid agonists and new agonist–antagonist analgesics contain not only useful reviews of the recent changes in pharmacokinetic and pharmacodynamic thinking, but excellent summaries of some of the newer compounds such as trefentanil, remifentanil, mirfentanil, ciramadol, tramadol and dezocine. Obviously, the pharmacodynamic effects of opioids are similar, with many differences related to changes in the pharmacokinetic characteristics of the drugs. However, the concise summaries are a useful source of information on the differences between new drugs, compared with long individual summaries with no comparative data.

In further contrast, the chapter on nitric oxide provided an excellent formal review of its endogenous role, evidence for selective pulmonary vasodilatation in animal studies and administration in humans as a vasodilator in patients with pulmonary hypertension, as a bronchodilator and in the treatment of hypoxaemia. The author readily recognizes that there are no blinded clinical trials which demonstrate a change in clinical outcome associated with the use of nitric oxide; however, the review provides an excellent starting point to develop such work.

As is common with a book of this type, different sections are appealing to some and not to others. However, the inclusion of broader "medical" reviews such as calcium channel blockers and anaesthetic topics of general relevance such as blood substitutes and α_2 blockers should ensure that the book has a deserving place on library shelves as long as "teachers" and "students" recognize that they may be working from the same volume!

J. E. Peacock

Basics of Transoesophageal Echocardiography. T. D. RAFFERTY (editor). Published by Churchill Livingstone, New York. Pp. 264; indexed; illustrated. Price £65.00.

Transoesophageal echocardiography is receiving ever more attention as a pre-, intra- and postoperative diagnostic and monitoring tool. This book is therefore timely and is written specifically for anaesthetists. The purpose of the book, as defined in the preface, is two-fold. First, to provide the reader with a description of the technical aspects of a basic transoesophageal echocardiographic examination and second, to provide the novice and intermediate practitioner with a clinically orientated source of background information which is necessary for interpretation of the images. In the main, the book succeeds in these two objectives.

The text is divided into four main sections covering basic considerations, the methodology of a two-dimensional echocardiographic patient examination, a section on more specialized techniques and procedures, and finally three chapters on the use of contrast media and training. The diagrams in the book are outstanding in terms of their three-dimensional clarity of interpretation and I cannot think of any other text which provides a better description in terms of both diagrams and words of the way in which the various scan directions are achieved and what they reveal. The illustrations in the book are uniformly of a high quality and there are many which are accompanied by a line diagram to aid interpretation. For someone approaching the subject for the first time, the chapters on two-dimensional echocardiography are excellent. I think the content of the book would provide a good guide to the necessary content of a course on transoesophageal echocardiography for specialist cardiac anaesthetists.

The book does however assume a certain basic knowledge of ultrasound and how it is reflected from tissues and for a book which has the word "basics" in the title it could perhaps be expected that this information would be provided. Consequently, although the book is extremely good in what it sets out to achieve, it would be necessary for someone wishing to obtain a grasp of the subject first to peruse the chapters of a more basic ultrasound text. I also believe that the section on quality assurance should have been introduced at an earlier stage. The need for training and the importance of the dangers of misinterpretation of images is of great importance in this subject. Although these points are made in the last chapter, they could have had more time allocated to them and, in particular, the dangers of misinterpretation given more prominence.

In summary, despite these drawbacks, this book fulfils a definite market need, and it is written by an anaesthetist. Because of this, the text is directed specifically at what anaesthetists and intensivists need to know, and the sections of text describing the various clinical aspects of the subject are in the appropriate proportions. In my view, it would form a valuable addition to the library of any cardiothoracic unit responsible for teaching trainees or any anaesthetist wishing to assess the value of transoesophageal echocardiography in clinical practice.

P. Hutton

Modulation of the Inflammatory Response in Severe Sepsis. J. M. TELLADO, R. A. FORSE AND J. S. SOLOMBIN (editors). Published by Karger, Switzerland. Pp. 188; indexed; illustrated. Price US$ 165.25.

This book is based on the International Symposium held in Madrid in 1993, which discussed modulation of the inflammatory response in severe sepsis. The book consists of 14 main chapters and three appendices. Each chapter is self-contained. The book does not unfold as a continuum but rather as a series of independent reviews.

The breadth and depth of material covered in the book are impressive, extending far beyond the relatively narrow areas of discussion found in mainstream reviews. An introductory chapter describes sepsis in terms of its current definition; this is a clear, easy to read chapter. Subsequently, each chapter covers different aspects of the inflammatory response. These range from the intracellular actions of endotoxins through inducibility of nitric oxide synthase and the role of neutrophils, to more erudite topics such as the influence of agents on the adhesion molecules that allow neutrophil migration.

Interspersed among these topics are chapters on the role of preclinical testing of drugs and design problems in clinical trials for antisepsis drugs. These seem to have appeared almost randomly, but as each chapter stands alone it does not influence the way in which the book is read. The chapters themselves are extremely informative.

This book would be of interest to the research orientated doctor in intensive care. The depth and detail of basic science are impressive. It is an excellent reference manual and provides a good dissertation on the understanding of the inflammatory response in 1993. A criticism of this type of book is always that by the time it is published the field has already moved on, but much of what I read in this book was completely new to me. The reference sections are good and therefore this is an extremely useful book to have on the shelf if the department has an interest in research into the field of inflammatory response.

In summary, this is a book that emphasizes the huge gap between our clinical practice and basic science knowledge. It is a useful reference book for those interested in modulation of the inflammatory response and, in particular, for those with research interests in that field. It may suffer from rapid ageing as the information is already 2 years old. It is probably not a book for the average trainee.

N. Soni

Sedation and Analgesia in the Critically Ill. G. R. PARK AND R. N. SLADEN (editors). Published by Blackwell Science, Oxford. Pp. 216; indexed; illustrated. Price £39.50.

Sedation and analgesia are important areas of intensive care practice that have received little attention in the literature. An overview of this vitally important subject is most welcome and the editors have succeeded in their aim of creating a book aimed at clinicians treating patients. Numerous clinicians from both Europe and the Antipodes have been commissioned to write chapters expanding their own personal views and reviewing the existing literature.

The book is divided into two sections; the first covers the general principles of sedation and analgesia, including indications, pharmacology and assessment of sedation; the second focuses on different types of disease states describing the most effective management of sedation and analgesia in the presence of renal failure, respiratory failure, brain failure, sepsis and trauma. Although there is some inevitable overlap, each contribution is interesting and useful in its own right and the editors and authors are to be commended on the quality of their contributions.

It is my impression that clinical recommendations made about sedation and analgesia in the critically ill are more often based on personal bias and clinical experience rather than on scientific fact. This book provides the clinician with the information that is currently available to allow a rational approach to sedation and analgesia in this group of patients. Perusal of this book would allow a more rational approach to this often neglected area of clinical practice.

D. A. B. Turner

Anaesthesia: Review 11. L. KAUFMAN AND R. GINSBURG (editors). Published by Churchill Livingstone, Edinburgh. Pp. 244; indexed; illustrated. Price £28.95.

This 11th volume in the series is the last to be edited by Dr Kaufman. The format remains much as with previous editions. Dr Kaufman provides an extensive compilation of medical problems affecting anaesthesia in two introductory essays and a final concluding miscellany briefly reviewing a number of topics.

The remaining 10 essays provide valuable reviews on topics ranging from anaesthesia for laparoscopy and the role of transoesophageal echocardiography in anaesthesia to medicolegal problems in anaesthesia and premedication in children. All are practical topics and most clinical anaesthetists will find much to interest and educate themselves. All sections carry comprehensive reference lists.

The essays are valuable in effectively annotating the current literature. They will help candidates for clinical examinations, and the examiners, and keep the rest of us up to date. I hope that Dr Ginsburg will maintain the tradition.

J. Norman

A Practical Approach to Cardiac Anesthesia. F. A. HENSLEY JR AND D. E. MARTIN (editors). Published by Little, Brown and Company, Boston. Pp. 713; indexed; illustrated. Price £52.50.

The aim of this American book is to help the anaesthetist to prepare for and manage cardiac anaesthesia. It is targeted for use in the operating department and intensive care unit by trainees and experienced anaesthetists, and the authors also suggest that it may be a valuable resource for perfusionists. In this second edition, 49 North American authors have contributed to 26 chapters and four sections. The whole book is in note form with many subtitles and lists. It is not referenced comprehensively but there is a suggested reading list at the conclusion of each chapter.

The first section (nine chapters) deals with the anaesthetic management for cardiac surgery, but the information is repeated in several chapters. It represents North American practice, often describes the practice of the individual author(s) and concentrates inadequately on management principles. The chapter on cardiovascular drugs has been expanded since the first edition to include many new drugs. Drugs are grouped according to their physiological properties and then presented alphabetically so that pharmacologically related drugs are separated. However, by relying on the comprehensive index at the start, the chapter becomes more accessible. There is also a chapter on monitoring which is clear and concise.

The second section (six chapters) concentrates on the anaesthetic management of specific cardiac disorders. It includes useful chapters on ischaemic, valvular and congenital heart disease, heart transplantation, electrophysiological disorders and coagulation management. There is also a chapter on surgical emergencies which is of limited value and strays into emergencies which are more appropriate to a book on thoracic anaesthesia.

It is not until the third section (seven chapters) that the basic equipment and techniques of cardiopulmonary bypass are described. The reason for this late introduction is to link in with chapters on mechanical life support devices, and adult and paediatric extracorporeal membrane oxygenation, that is techniques which owe their development to perfusion technology. In this section there are also chapters on the pathophysiology of cardiopulmonary bypass, myocardial and cerebral protection.

The final section (three chapters) contains a useful chapter on thoracic aneurysms and dissections. The final two chapters on the management of thoracic anaesthesia and its pain management are inadequate and (I think) redundant within this book.

The book contains a lot of information within its 700 pages. Its presentation in note form and duplication of information in chapters make it difficult to read and prevent its use as a textbook. However, it was not designed as such. If, as the authors suggest, it is sited within the cardiac unit it will be used as a reference to obtain rapid information on immediate clinical problems.

K. M. Sherry

ERRATUM

British Journal of Anaesthesia 1995; 75: 664P

In the abstract by Driver and colleagues, an error arose in the reported dose of propofol in the second paragraph:
"group 2 received alfentanil 10 μg kg^{-1} 90 s preinduction followed by propofol 2.5 mg kg^{-1}" should read "group 2 received alfentanil 10 μg kg^{-1} 90 s preinduction followed by propofol *1.25 mg* kg^{-1}".

We apologize to the authors for this confusion.

Papers for publication and all editorial communications should be addressed to:
Professor G. Smith,
Editor, British Journal of Anaesthesia,
University Department of Anaesthesia,
Leicester Royal Infirmary,
Leicester LE1 5WW.
Telephone: 0116 247 0141
Fax: 0116 285 4487

All **business communications** should be sent to the Publishers: Professional & Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR.

The GUIDE TO CONTRIBUTORS may be found in the advertisement section of any issue of the journal (pages ii, iv & vi).
Published monthly. Annual subscriptions: Worldwide £156.00; USA only $245.00 (direct orders only). Trainee rate: Worldwide £75.00. Airmail rates on application. ISSN 0007–0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR. Orders in the USA may be sent to Professional and Scientific Publications, PO Box 408, Franklin, MA 02038, USA.

"WIREX" self-binding cases, which hold a complete volume, i.e. 6 months with room for a supplement and annual handbook, are now available. Price UK £14.00 per two binders, Europe £20.00 per two binders (to cover 1 year). Price includes postage and packing. Rest of the World prices on application. Cheque with order to Hethersett Supplies, Mount Bovers Lane, Hawkwell, Essex SS5 4JA, Tel. (01702) 202393.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statements appear in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statements. Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

© Copyright: 1996 *British Journal of Anaesthesia*
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia*, requests for which should be addressed to the **Publishers**.

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge.

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 76, No. 2 FEBRUARY 1996

EDITORIAL

Prospects for management of peripheral vascular failure in septic shock

Sepsis remains a major cause of death in intensive care units [1], commonly as the final complication of serious illness, despite adequate antibiotic treatment. Has clinical science any useful new insights into this major medical problem?

The endothelium-derived relaxing factor in blood vessels, reported in 1980 [2], was established later to be nitric oxide or a nitrosothiol. The effects of nitric oxide in regulating vascular tone, platelet function, neurotransmission and host defence have been reviewed recently in this journal [3]. These findings have led to major re-evaluation of the physiological control mechanisms in the peripheral circulation in health and disease, a task by no means complete. So far deficient endothelial release of nitric oxide has been implicated in the pathogenesis of vascular disorders as diverse as hypertension, diabetes mellitus and hypercholesterolaemia [4, 5]. The endothelial or constitutive nitric oxide synthase enzyme (eNOS) continuously replaces this short-lived local regulator, with additional release in response to increased flow velocity in the vessel (shear stress), mechanical deformation or circulating vasodilators.

Excessive production of nitric oxide contributes to the clinical syndrome of gram-negative shock, by causing pathological vasodilatation and reducing the force of myocardial contraction [6]. The main links in this chain of events have been established in experimental animals. Bacterial endotoxin stimulates white cells to release cytokines [7], principally tumour necrosis factor-α (TNFα), interleukins and platelet activating factor (PAF). These cytokines in turn stimulate the expression of genes for inducible nitric oxide synthase (iNOS) in the endothelium, vascular smooth muscle and myocardium, causing overproduction of nitric oxide, which increases the intracellular concentration of cyclic guanosine monophosphate (cGMP) in these and adjacent cells. Vasodilatation results through effects on a variety of ion channels. Recent work implicated the opening of ATP-sensitive potassium channels in hyperpolarizing the smooth muscle cell and dilating the blood vessel. More widespread activation of iNOS has been observed in macrophages, neutrophils, lung, liver [8], kidney and skeletal muscle. This increase in nitric oxide may be in part protective [9].

Doubts have been expressed on the validity of animal models of endotoxaemia, or indeed the role of endotoxin in the clinical syndrome [10]. The current article by Tsuneyoshi, Kanmura and Yoshimura in this issue of the journal [11] establishes in human intestinal arteries *in vitro*, that endotoxin stimulates nitric oxide synthase in the smooth muscle of the vessel wall, in the absence of endothelium or many white cells, and that cGMP-mediated vasodilatation occurs with a loss of responsiveness to the vasoconstrictor actions of noradrenaline. Pretreatment with glucocorticoid reduced the vascular and biochemical changes and maintained responsiveness to noradrenaline. In accord with clinical experience of endotoxic shock, late treatment with glucocorticoids (6 h after endotoxin) was ineffective.

Attempts have been made to block this deleterious pathway at various steps. Competitive antagonism of nitric oxide synthase with analogues of its substrate L-arginine restores vascular responsiveness [12] and arterial pressure in experimental endotoxaemia, but does not necessarily improve the circulatory state of animals [13–15] or patients [3, 16]. Excessive vasoconstriction in the presence of a hypodynamic heart may restore arterial pressure but in doing so may reduce cardiac output further, leading to overall haemodynamic deterioration. Many years ago this problem limited the use of noradrenaline, metaraminol and other vasoconstrictor agents. There is experimental evidence that the excessive vasoconstriction and reduction in cardiac output caused by inhibition of nitric oxide synthase can be reversed in healthy anaesthetized pigs by the addition of selective arterial vasodilators, such as the calcium antagonist nicardipine [17] or the potassium channel opening drug levcromakalim [18]. These results suggested that peripheral resistance could be monitored and controlled at appropriate levels. However, it is less easy to achieve beneficial control and restore cardiac output in pigs treated with endotoxin [19].

The administration of methylene blue, the putative inhibitor of guanylate cyclase, had haemodynamic effects similar to those of inhibition of nitric oxide synthase in patients with septic shock [20].

Non-selective inhibition of nitric oxide synthase also blocks the cytoprotective effects of nitric oxide, and may aggravate tissue damage [9]. The development of drugs which specifically inhibit the inducible form of nitric oxide synthase may preserve the beneficial effects of the constitutive endothelial release of nitric oxide [3, 12, 16]. It remains to be seen whether or not this relatively selective approach will greatly improve the clinical management of established sepsis, as it ameliorates only one end result of many complex processes.

Prevention of the formation of the inducible nitric oxide synthase in vascular smooth muscle and myocardium should be more effective, but would require early intervention or pretreatment. Antibody to the stimulatory cytokines (e.g. anti-TNFα [21] or receptor antagonists to interleukin-1 [22] or PAF [23] reduced the effects of the administration of endotoxin to experimental animals. The clinical potential of such studies is supported by the correlation of lung injury and mortality with high blood concentrations of TNF in patients with septic shock [24]. The use of high doses of glucocorticoids for clinical management of septic shock was suggested 30 yr ago [25]. Among disparate actions, glucocorticoids reduce the expression of inducible nitric oxide synthase and cytokine release [26]. However, clinical experience has been highly variable, and controlled studies of the use of glucocorticoids have shown little benefit [27]. The direct intravascular measurement of nitric oxide in patients should result in more precise understanding of the cause and effect for better clinical management [28].

These developments in the understanding of cellular mechanisms and effects have not yet led to definitive treatment for this common and serious condition. However, there is optimism that further attack on the problem of septic shock with the new methods of molecular biology and cellular physiology will be successful. Advances in gene therapy may permit regulation of the induction of nitric oxide synthase, and control of intracellular mediators in this, as in other cardiovascular disorders [29].

J. D. ALLEN
Physiology Department
The Queen's University of Belfast
97 Lisburn Road
Belfast BT9 7BL
N. A. HERITY
Regional Medical Cardiology Centre
The Royal Victoria Hospital
Grosvenor Road
Belfast BT12 6BA

References

1. Parillo JE, Parker MM, Natanson C, Suffredini AF, Danner RL, Cunnion RE, Ognibene FP. Septic shock in humans. *Annals of Internal Medicine* 1990; **113**: 227–242.
2. Furchgott RF. The discovery of endothelium-dependent relaxation. *Circulation* 1993; **87** (Suppl. V): V3–V8.
3. Quinn AC, Petros AJ, Vallance P. Nitric oxide: an endogenous gas. *British Journal of Anaesthesia* 1995; **74**: 443–451.
4. Meredith IT, Yeung AC, Weidinger FF, Anderson TJ, Uehata A, Ryan TJ, Selwyn AP, Ganz P. Role of impaired endothelium-dependent vasodilation in ischemic manifestations of coronary artery disease. *Circulation* 1993; **87** (Suppl. V): V56–V66.
5. Cohen RA. Dysfunction of vascular endothelium in diabetes mellitus. *Circulation* 1993; **87** (Suppl. V): V67–V76.
6. Brady AJB, Poole-Wilson PA. Circulatory failure in septic shock. Nitric oxide: too much of a good thing. *British Heart Journal* 1993; **70**: 103–105.
7. Raetz CRH, Ulevitch RJ, Wright SD, Sibley CH, Ding A, Nathan CF. Gram-negative endotoxin: an extraordinary lipid with profound effects on eukaryotic signal transduction. *FASEB Journal* 1991; **5**: 2652–2660.
8. Knowles RG, Merrett MS, Moncada S. Differential induction of brain, lung and liver nitric oxide synthase by endotoxin in the rat. *Biochemical Journal* 1990; **270**: 833–836.
9. Cooke JP, Tsao PS. Cytoprotective effects of nitric oxide. *Circulation* 1993; **88**: 2451–2454.
10. Hurley JC. Reappraisal of the role of endotoxin in the sepsis syndrome. *Lancet* 1993; **341**: 1133–1135.
11. Tsuneyoshi I, Kanmura Y, Yoshimura N. Methylprednisolone inhibits endotoxin-induced depression of contractile function in human arteries *in vitro*. *British Journal of Anaesthesia* 1996; **76**: 251–257.
12. Stoclet JC, Fleming I, Gray G, Julou-Schaeffer G, Schneider F, Schott C, Schott C, Parratt JR. Nitric oxide and endotoxemia. *Circulation* 1993; **87** (Suppl. V): V77–V80.
13. Klabunde RE, Ritger RC. N^G-monomethyl-L-arginine (NMA) restores arterial blood pressure but reduces cardiac output in a canine model of endotoxic shock. *Biomedical and Biophysical Research Communications* 1991; **178**: 1135–1140.
14. Wright CE, Rees DD, Moncada S. Protective and pathological roles of nitric oxide in endotoxin shock. *Cardiovascular Research* 1992; **26**: 48–57.
15. Robertson FM, Offner PJ, Ciceri DP, Becker WK, Pruitt BA. Detrimental hemodynamic effects of nitric oxide synthase inhibition in septic shock. *Archives of Surgery* 1994; **129**: 149–156.
16. Petros A, Lamb G, Leone A, Moncada S, Bennett D, Vallance P. Effects of a nitric oxide synthase inhibitor in humans with septic shock. *Cardiovascular Research* 1994; **28**: 34–39.
17. Herity NA, Allen JD, Silke B, Adgey AAJ. Comparison of the ability of nicardipine, theophylline and zaprinast to restore cardiovascular haemodynamics following inhibition of nitric oxide synthesis. *British Journal of Pharmacology* 1994; **112**: 423–428.
18. Herity NA, Allen JD, Silke B, Adgey AAJ. Assessment of levcromakalim and sodium nitroprusside to reverse the cardiovascular effects of nitric oxide synthase inhibition in the anaesthetised pig. *Cardiovascular Research* 1994; **28**: 894–900.
19. Herity NA, Allen JD, Silke B, Adgey AAJ. Haemodynamic effects of nitric oxide synthase inhibition in healthy pigs and in an improved porcine model of endotoxic shock. *European Heart Journal* 1995; **16** (Suppl.): 312.
20. Schneider F, Lutun P, Hasselmann M, Stoclet JC, Tempe JD. Methylene blue increases systemic vascular resistance in human septic shock. *Intensive Care Medicine* 1992; **18**: 309–311.
21. Thiemermann C, Wu CC, Szabo C, Perretti M, Vane JR. Role of tumour necrosis factor in the induction of nitric oxide synthase in a rat model of endotoxin shock. *British Journal of Pharmacology* 1993; **110**: 177–182.
22. Ohlsson K, Bjork P, Bergenfeldt M, Hageman R, Thompson RC. Interleukin-1 receptor antagonist reduces mortality from endotoxin shock. *Nature (London)* 1990; **348**: 550–552.
23. Szabo C, Wu CC, Mitchell JA, Gross SS, Thiemermann C, Vane JR. Platelet-activating factor contributes to the induction of nitric oxide synthase by bacterial lipopolysaccharide. *Circulation Research* 1993; **73**: 991–999.
24. Marks JD, Marks CB, Luce JM, Montgomery AB, Turner J, Metz CA, Murray JF. Plasma tumor necrosis factor in patients with septic shock. Mortality rate, incidence of adult respiratory distress syndrome and effects of methylprednisolone administration. *American Review of Respiratory Disease* 1990; **141**: 94–97.
25. Lillehei RC, Longerbeam JK, Bloch JH, Manax WG. The nature of irreversible shock: experimental and clinical observations. *Annals of Surgery* 1964; **160**: 682–710.
26. Radomski MW, Palmer RMJ, Moncada S. Glucocorticoids inhibit the expression of an inducible, but not the constitutive, nitric oxide synthase in vascular endothelial cells. *Proceedings of the National Academy of Sciences, USA* 1990; **87**: 10043–10047.
27. Slotman GJ, Fisher CJ, Bone RC, Clemmer TP, Metz CA, The Methylprednisolone Severe Sepsis Study Group. Detrimental effects of high-dose methylprednisolone sodium succinate on serum concentrations of hepatic and renal function indicators in severe sepsis and septic shock. *Critical Care Medicine* 1993; **21**: 191–195.
28. Vallance P, Patton S, Bhagat K, MacAllister R, Radomski M, Moncada S, Malinski T. Direct measurement of nitric oxide in human beings. *Lancet* 1995; **345**: 153–154.
29. Ludwig S, Rapp UR. Cascading towards vascular disorder gene therapy. *Nature Medicine* 1995; **1**: 513–515.

British Journal of Anaesthesia 1996; **76**: 179–185

CLINICAL INVESTIGATIONS

Effect of age on MAC in humans: a meta-analysis

W. W. MAPLESON

Summary

It is well known that MAC, the minimum alveolar concentration required to prevent movement in response to surgical incision in 50% of patients, decreases with age. Regression analysis showed that data for humans derived from a comprehensive literature survey were consistent, for age > 1 yr, with $\log_{10}$ MAC decreasing with increasing age at the same rate for all inhaled anaesthetics; approximately equivalent to 6% change per decade of age. With some slight reservation on differences between data from different institutions, the present data for humans are consistent (for age > 1 yr) with the equation $\text{MAC} = a \times 10^{bx}$ where x = difference in age (in years) from 40, $b = -0.00269$ (95% confidence limits (CL) −0.0030, −0.0024) and a = MAC at age 40 yr, which, for anaesthetics currently in use clinically, is given by: halothane, 0.75%; isoflurane, 1.17%; enflurane, 1.63%; sevoflurane, 1.80%; desflurane 6.6%; nitrous oxide, 104%; with 95% CL of approximately ±7% (±10% for desflurane, ±17% for enflurane). (*Br. J. Anaesth.* 1996; **76**: 179–185)

Key words

Anaesthetics gases. Anaesthetics volatile. Potency, anaesthetic, MAC. Age factors.

MAC has been defined as "the minimum alveolar concentration of anaesthetic at 1 atmosphere that produces immobility in 50 per cent of those patients or animals exposed to a noxious stimulus" [1]. There is the rider [1] that the alveolar concentration must have been held constant for long enough for the brain to come into equilibrium with the alveolar concentration. In humans, the stimulus is normally surgical incision.

It is well known that MAC decreases with age and some authors [2–5] have drawn attention to similarities between agents in the trend of MAC with age. A need to express measured end-tidal concentrations of halothane, enflurane and isoflurane in terms of MAC units in patients of different ages [6] provided the stimulus to try to derive, from published data, a general equation to represent the dependence of MAC on age. Thus, in the terms of Andersen [7], this is an "inductive, hypothesis-generating" study, not a hypothesis-testing one.

Methods

SELECTION OF DATA FOR ANALYSIS

The selection was restricted to peer-reviewed investigations which used inhalation induction and, with one exception, no premedication or only atropine, and which reported, for each group studied, the number of patients, mean age and the value of MAC derived. Data for alternative forms of MAC, such as MAC for tracheal intubation [8], and MAC based on "grimace or movement" [9] rather than only on movement, were excluded: although the dependence of the grimace variant of MAC on age seems very similar to that of conventional MAC, MAC for tracheal intubation under sevoflurane appears to *increase* with age [10, 11]. Similarly, values for MAC derived from movement in response to electrical stimulation were excluded because there is some evidence [12] that they may not be consistent with values based on response to surgical incision.

Literature searches in the Embase and Medline databases, together with examination of the citations in the resulting papers, yielded a total of 30 articles [2–5, 10–35] containing data that met the selection criteria. These included nine articles from which indirect estimates of MAC for nitrous oxide were derived (appendix). Direct estimate in volunteers at hyperbaric pressures [36] was not used because this was based on the response to electrical stimulation.

STRATEGY FOR COMBINING DATA FROM DIFFERENT STUDIES

Only one article [12], from Berne at 500 m above sea level, reported a correction (−6% of MAC) for altitude, as the definition of MAC is in terms of the concentration of anaesthetic *at 1 atmosphere* [1]. For the present study, corrections were also applied to results from studies conducted at more than 100 m above sea level: Iowa −2.5%; Durham, North Carolina (Duke University), −1.5%; Milan −1.5%.

All estimates of MAC were included in a multiple linear regression analysis. Because of the wide range of MAC values between different anaesthetics (more than 100 to one), $\log_{10}$ MAC was used as the dependent variable. Individual estimates of MAC were generally weighted in proportion to the number of patients included in each group (appendix).

W. W. MAPLESON, DSC, FINSTP, Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Cardiff CF4 4XN. Accepted for publication: October 2, 1995.

Inspection of the data suggested that values of MAC for children, especially those less than 1 yr of age, might be inconsistent with the trend for adult data; therefore analyses were performed for all ages, age > 1 yr and age > 18 yr.

For each of these three analyses, three versions of the regression were tried, on the basis of three different assumptions.

(1) All estimates of MAC for a given anaesthetic are equally valid (apart from the weighting). For this version, a set of parallel lines was fitted, one for each anaesthetic. This used all of the data.

(2) There may be differences between institutions because of slightly different techniques or because different populations were sampled. This version required a separate parallel line for each institution within each anaesthetic. This is equivalent to basing the slope only on data from those institutions that have studied more than one age group.

(3) There may be differences even between studies within the same institution. This version required a separate parallel line for each study. It involved basing the slope only on data which included more than one age group in a single study.

Within each of these three versions, evidence of curvature of the regression of log MAC on age was sought by adding $(\text{age})^2$ and $(\text{age})^3$ to the predictor terms, and evidence of differences between anaesthetics in the dependence of log MAC on age by allowing a separate slope for each agent.

Each elaboration or restriction of the model was tested for improvement of fit and adopted only if it yielded $P < 0.05$. This is a regression equivalent of a procedure [37] for testing for consistency of groups in a meta-analysis of means.

Further inspection of the data showed that only one study (for halothane [14]) included data for children in addition to adults, and that this study would have a dominant effect on the results of the one-line-per-study analyses. However, there were two instances where one anaesthetic (sevoflurane) was the subject of two studies from the same institution, with one or more authors in common, published in the same or consecutive years, with one dealing with children and the other with adults. Therefore, for the purpose of the analyses, each of these pairs of studies ([10, 11] and [5, 27]) was treated as a single study.

The statistical package used was GLIM 4, [38, 39] update 8, on a DEC mainframe computer under the Ultrix operating system OSF/1 V3.0.

Results

The input data derived from the literature survey are listed in table 1.

Table 1 Data derived from the literature. w = Weight assigned to each MAC value, usually the number of patients involved, but see appendix. UCSF = University of California, San Francisco; UCSD = University of California, San Diego; Univ. = university. *Individual age data available. †The negative ages refer to preterm neonates and correspond to the degree of prematurity. MAC values are generally as quoted in the original references (for a logistic regression estimate where there was a choice) but reduced to sea level for institutions above 100 m altitude (see appendix for nitrous oxide values)

Anaesthetic and institution	w	Mean age (yr)	MAC (%)	Reference
Methoxyflurane				
UCSF, USA	17	37.3	0.16	[13]*
Halothane				
UCSF, USA	12	0.2	1.08	[14]
	14	1.5	0.97	[14]
	19	4.1	0.91	[14]
	8	8.4	0.87	[14]
	11	15.5	0.92	[14]
	22	24.9	0.84	[14]
	24	42.0	0.76	[14]
	10	81.4	0.64	[14]
	24	42.0	0.765	[13]*
	28	38.9	0.75	[15]
	18	39	0.73	[16]
	12	0.03	0.87	[17]
	12	0.3	1.20	[17]
US navy, San Diego, USA	16	20.6	0.73	[18]
Univ. of Iowa, USA	11	1.2	0.92	[19]
Isoflurane				
UCSF, USA	16	26.1	1.28	[4]
	32	44.2	1.15	[4]
	30	64.0	1.05	[4]
	12	0.04	1.60	[20]
	12	0.3	1.87	[20]
	12	0.75	1.80	[20]
	12	2.0	1.60	[20]
	12	4.0	1.60	[20]
Duke University, USA	18	36.0	1.21	[21]
Univ. of Bristol, UK	72	55.0	1.00	[22]
Univ. of Toronto, Canada	20	−0.15†	1.28	[23]
	16	−0.10†	1.41	[23]
Univ. of Iowa, USA	11	1.4	1.65	[24]
Univ. of Berne, Switzerland	17	39.7	1.16	[12]
Enflurane				
Univ. of Miami, USA	19	38.9	1.68	[25]*
Univ. of Milan, Italy	8	36.5	1.58	[26]*
Sevoflurane				
Hamamatsu Univ., Japan	20	4.3	2.49	[27]*
	20	47.6	1.71	[28]*
	20	71.4	1.48	[5]*
UCSD, USA	16	38.0	2.05	[29]*
Metropolitan Geriatric Hospital, Tokyo, Japan	24	82.0	1.22	[30]*
Saiseikai General Hospital, Mito, Japan	22	4.6	2.03	[10]
	42	48.7	1.58	[11]
Univ. of Toronto, Canada	12	0.04	3.30	[31]
	12	0.20	3.20	[31]
	12	0.6	2.50	[31]
	12	1.7	2.60	[31]
	12	3.9	2.50	[31]
	12	7.7	2.50	[31]
Diethyl ether				
UCSF, USA	17	36.5	1.92	[13]*
Fluroxene				
UCSF, USA	15	44	3.4	[32]
Desflurane				
UCSF, USA	9	25.6	7.25	[3]
	11	48.0	6.00	[3]
Univ. of Miami, USA	18	69.6	5.17	[33]
Univ. of Toronto, Canada	12	0.04	9.29	[34]
	12	0.23	9.39	[34]
	12	0.7	9.96	[34]
	12	1.8	8.73	[34]
	12	3.7	8.54	[34]
	12	7.5	8.16	[34]
Cyclopropane				
UCSF, USA	16	32	9.80	[2]
	12	81	7.60	[2]
	19	44	9.20	[13]
Ethylene				
US navy, San Diego, USA	20	23.1	67	[18]
Xenon				
UCSF, USA	28	43.2	71	[35]
Nitrous oxide				
UCSF, USA	8.2	25.9	120	[4]
	13.7	45.1	120	[4]
	13.9	65.2	104	[4]
	6.7	43.6	98	[32]
	4.2	25.1	125	[3]
	6.5	44.7	107	[3]
Univ. of Milan, Italy	8.0	36.5	101	[26]*
Univ. of Miami, USA	9.7	69.6	85	[33]
Hamamatsu Univ., Japan	10.0	46.0	103	[28]
Univ. of Iowa, USA	19.0	1.2	102	[19]
	17.6	1.4	106	[24]
Univ. of Toronto, Canada	6.0	1.8	247	[31]

Regression analyses showed that, whichever age range was included (all, > 1 yr, > 18 yr), it was essential to allow a separate line for each institution (P always < 0.0006) but not for each study (P always > 0.06). With one line per institution (or one per study) there was a strong improvement in fit by restricting age to > 1 yr ($P < 0.0001$) but little further improvement on restricting to > 18 yr ($P > 0.09$). There was no significant curvature in any

Table 2 Fitted MAC at ages 1, 40 and 80 yr (based on data for age > 1 yr) with confidence limits (CL). w = Total weight (see appendix) for each anaesthetic (or institution). MAC for other ages (> 1 yr) can be calculated according to equation (2) where b is given by equation (1), x = difference in age (in years) from 40 yr, and $a(i,j)$ = MAC at age 40 yr for anaesthetic i and (where appropriate) institution j. *Institution (see table 1)—where more than one institution has reported MAC values for age > 1 yr. †CL at 1 and 80 yr are up to 1 % of MAC greater. ‡Single MAC value for each age, based on all data for that anaesthetic for age > 1 yr

Anaesthetic and institution*	w	MAC (%) at specific ages (yr)			95 % CL at age 40 yr (% of MAC)†
		1	40	80	
Methoxyflurane	17	0.200	0.157	0.123	21
Halothane					
UCSF	178		0.76		
US navy	16		0.65		
Iowa	11		0.72		
Global‡	205	0.95	0.75	0.58	6
Isoflurane					
UCSF	102		1.21		
Duke	18		1.18		
Bristol	72		1.10		
Iowa	11		1.30		
Berne	17		1.16		
Global‡	220	1.49	1.17	0.91	6
Enflurane					
Miami	19		1.67		
Milan	8		1.55		
Global‡	27	2.08	1.63	1.27	17
Sevoflurane					
Hamamatsu	60		1.86		
UCSD	16		2.02		
Tokyo	24		1.58		
Mito	64		1.66		
Toronto	36		2.03		
Global‡	200	2.29	1.80	1.40	6
Diethyl ether	17	2.39	1.88	1.47	21
Fluroxene	15	4.4	3.5	2.7	22
Desflurane					
UCSF	20		6.4		
Miami	18		6.2		
Toronto	36		6.8		
Global‡	74	8.3	6.6	5.1	10
Cyclopropane	47	12.1	9.5	7.4	13
Ethylene	20	77	60	47	19
Xenon	28	92	72	57	16
Nitrous oxide					
UCSF	53.2		115		
Milan	8.0		99		
Miami	9.7		102		
Hamamatsu	10.0		107		
Iowa	36.6		82		
Toronto	6.0		195		
Global‡	123.5	133	104	81	8

model, except for one line per institution using all ages ($P = 0.03$), nor any significant difference in slope between anaesthetics.

Thus the optimum model was that with the data restricted to age > 1 yr, and with a separate parallel straight line for each institution for each anaesthetic. This gave a slope of $\log_{10}$ MAC on age of:

$$b = -0.00269\ \text{yr}^{-1} \qquad (1)$$

with 95 % confidence limits (CL) of −0.0030 and −0.0024, that is ±12 %. This corresponds to a change in MAC of approximately 6 % per decade of age or, more precisely, a 22 % decrease from 40 to 80 yr of age and a 27 % increase from 40 to 1 yr of age.

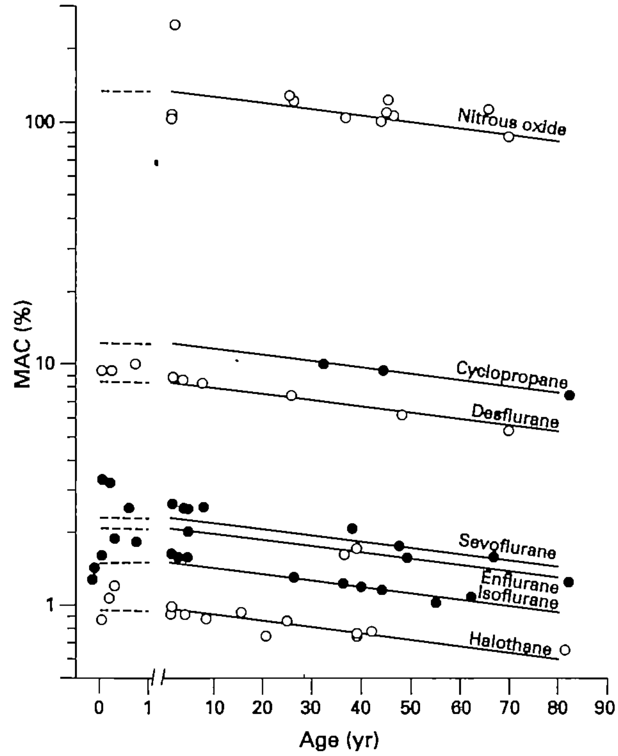


Figure 1 Effect of age on MAC: comparison of fitted lines with published values. Continuous lines = fitted values, from 1 to 80 yr, for each anaesthetic as a whole, based on data for age > 1 yr; broken lines = extrapolation to age zero. The bias and extra scatter of published values about these extrapolations draw attention to their invalidity (see text). A 10-times expanded time scale has been used for ages less than 1 yr to separate the many published values in that age range. The symbols, (○) and (●) are used for alternate anaesthetics. Five agents are omitted to avoid cluttering the diagram: for each agent, only a single estimate of MAC was available and the fitted line necessarily went through that value.

To avoid explicitly stating a notional, but misleading, MAC at age 0, it is preferable to express the results relative to MAC at some intermediate age. Forty years has been chosen as a convenient midpoint. Thus, the overall results can best be summarized by the equation:

$$\text{MAC} = a(i,j) \times 10^{bx} \qquad (2)$$

where x = *difference* in age (in years) from 40 yr, b = slope of $\log_{10}$ MAC on age (equation (1)), and $a(i,j)$ = fitted value of MAC at 40 yr of age for anaesthetic i and (where appropriate) institution j (table 2). It must be stressed that the equation is not valid for age < 1 yr. The residual SD of the data points about the fitted lines was 0.0179 in terms of $\log_{10}$ MAC, corresponding to 95 % of the points lying within ±8 % of the one-line-per-institution predicted values.

The implications of this equation are illustrated in table 2, which lists fitted values of MAC for each institution at 40 yr of age and for each anaesthetic as a whole at ages 1, 40 and 80 yr. These "global" values were obtained by forcing the fitted slope (equation (1)) on all data for each anaesthetic but allowing only a single intercept—a single $a(i)$. Confidence intervals (95 %) are given for 40 yr of age; confidence intervals at ages 1 and 80 yr are up to 1 % of MAC greater. With these global lines (one per anaesthetic) the discrepancies between institutions have increased the residual SD of the data points to 0.0453, corresponding to 95% of the points lying within −18%, +23% of the global, one-line-per-anaesthetic, predicted values. Strictly, this applies only to points which have the average weight (for age > 1 yr) of 17; points with lower weight ("w" in table 1), as with many of the nitrous oxide values, have a wider scatter and vice versa.

Conformity of the original data to the fitted regression lines is shown in figure 1. The main part of the graph shows measured values and fitted lines for age > 1 yr; the left of the graph shows extrapolation to zero age (broken lines), and measured values for age < 1 yr, on a 10-times expanded age scale (hence the flatter slope of the broken lines). To avoid cluttering the graph, data for five agents have been omitted: each of those lines would simply go through the one measured value.

Discussion

The available data are consistent with the hypothesis that all inhaled anaesthetics have a common slope of $\log_{10}$ MAC on age, for age > 1 yr, but that there may be differences between institutions in MAC for an anaesthetic, for any particular age. A theory of why a common slope is not surprising is given in the appendix.

A common slope for *log* MAC on age is consistent with the findings that the change in linear MAC with age is the same for several agents only if MAC for each agent, at any age, is expressed as a percentage of MAC for that agent at some standard age [2, 3], or if some equivalent scaling manoeuvre is used [4, 5].

These findings are not contradicted by the observation [3] that the slope of MAC on age for a volatile anaesthetic, when combined with a fixed concentration of nitrous oxide, is steeper than that for the volatile alone. This arises because the fixed concentration of nitrous oxide represents a larger fraction of MAC at the greater age; therefore a smaller fraction of MAC needs to be supplied by the volatile agent.

The difference in fitted MAC between institutions might be attributable to the sampling of different populations. There is some evidence in table 2 of MAC values from North America being greater than those from Europe (isoflurane and enflurane) or Japan (sevoflurane), but there are comparable or wider differences between institutions within North America (halothane, isoflurane, desflurane and nitrous oxide) or Japan (sevoflurane). Also, part of the difference in the case of isoflurane could be attributed to the use of temazepam 20 mg orally as premedication in one of the European studies [22]. Therefore, the differences may all be attributable to slight variations in technique, including differences in the absolute calibration of the gas analysers used. It is on this basis that a "global" value is given for each of these anaesthetics in table 2 and global fitted lines are plotted in figure 1.

It is the residual SD of the (age > 1 yr) data points around these global lines (corresponding to 95% of the points lying within approximately ±20% of the predicted values) which has been used in calculating the confidence limits in table 2. Apart from a small addition arising from uncertainty over the slope of the dependence on age, the confidence limits at age 40 yr, as a percentage of MAC, are equal to approximately $20 \times \sqrt{(17/w)}$, where w = total weight for the anaesthetic (usually the number of patients studied) and 17 is the average weight per MAC value in table 1 for age > 1 yr. For each anaesthetic which has been the subject of only one study, with 15 to 28 patients, the confidence limits are considerably wider than any derivable from the study itself. This is because the confidence limits in table 2 allow for the general variability between studies and between institutions, which variability is absent from the results of any one study.

The left-hand part of figure 1 shows that, for ages less than 1 yr, the proportion of measured values lying within −18%, +23% of the extrapolations of the regression lines is not 95% but only 70% (10 of 14). Until recently it was possible to argue [34] that there was a consistent trend for young children, with MAC reaching a peak at around 6 months of age, but recent data on sevoflurane in this age range [31] appear to contradict this. The poor agreement with extrapolations of the global lines could be reduced by postulating a steepening of the lines in the early years of life. Certainly, the mainly non-significant curvatures found in the regression analyses were mostly in this direction. The remainder of the scatter could then be attributed to most of these MAC values being based on only 12 patients each, instead of the mean of 17 for age > 1 yr. However, it is clear that further studies in this age range, with larger numbers of patients, are needed to resolve the discrepancies.

As MAC is defined in terms of anaesthetic concentration at 1 atmosphere, corrections should be applied, not only for the systematic effect of altitude (as was done in this analysis), but also for day-to-day variations in barometric pressure. This could not be done because none of the studies reported barometric pressure. The range of barometric pressure amounts to about ±5% (about 95–105 kPa at sea level), but each study would be spread over at least several days so that mean pressures for different studies would generally vary less than this. Therefore, this can account for only a small fraction of the scatter in figure 1. However, it is probably unwise to draw conclusions from differences of less than 5% between studies.

A further source of uncertainty is the difference between end-tidal and arterial partial pressure because it is the latter with which the site of action of the anaesthetic will equilibrate. This difference can be expected to vary with the degree of ventilation–perfusion mismatch in the lungs and so account for some of the scatter in figure 1. However, even if all studies were carried out in terms of arterial partial pressure, this would not be very helpful clinically because such measurements are not generally available.

A few studies (* in table 1) reported full data for each individual patient: end-tidal concentration, age and whether or not the patient moved. With such data it is possible, in principle, to obtain an estimate of MAC, and also its dependence on age, from a single study. This can be done using logistic regression or probit analysis to predict "not move" from both log concentration and age. When this was tried, it was found that most individual studies failed to show a significant dependence on age because each covered only a small range of ages. However, combining the results from the nine groups of patients receiving only a volatile anaesthetic, and using a separate intercept for each institution, gave a slope of $-0.00288 \log_{10}$ MAC yr^{-1} compared with the present -0.00269, and confidence limits of $\pm 27\%$ (based on 182 patients, a weight of 182 as defined in the appendix) compared with the present $\pm 12\%$ (around one line per institution and based on a weight of 993).

The ratio of these two percentage confidence limits (2.25) is nearly the same as the ratio of the square roots of the two weights (2.34), and therefore overall there is no particular advantage in one technique over the other. However, the logistic or probit technique would have an advantage within a single large study: if it is desired to determine MAC for a range of ages, the current procedure is to study say 20 patients in each of three or four age groups, determine MAC for each group, and perhaps fit a line to the three or four results leading to a slope with a standard error which would have only one or two degrees of freedom. Instead, it would be better to handle all the results in one analysis to predict the probability of movement from log concentration and age so that the standard error of the slope on age would have almost as many degrees of freedom as the number of patients studied.

Stewart and Parmar [40] have demonstrated the advantages of "meta-analysis of individual-patient data" (MAP) compared with "meta-analysis of the literature" (MAL) in the context of survival studies. The main analysis in this article, using just MAC and mean age from each study group, is an example of MAL; logistic analysis of those studies which gave full data on individual patients is an example of MAP. Therefore, the fact that the two "MAP/MAL" ratios (ratio of percentage confidence limits and ratio of the square roots of the weights) were so similar suggests that MAP has no advantage over MAL in the present context, unless additional information was obtained from the original authors, as Stewart and Parmar did.

In conclusion, it is suggested that the parallel lines defined by equations (1) and (2), and the numerical values in table 2, represent the current best estimates of MAC, and its dependence on age, for the 12 inhaled anaesthetics listed, and for age > 1 yr. However, the present data allowed only limited testing of differences in slope between anaesthetics or in intercept between institutions or studies so it may be that, as more data are accumulated, the true picture will prove to be more complex. In the meantime, the present global regression lines provide a consistent basis for expressing measured concentrations of these anaesthetics as fractions or multiples of MAC at any age > 1 yr. The lines are typified by the values for isoflurane: MAC = 1.49% at age 1 yr, 1.17% at 40 yr and 0.91% at 80 yr.

Appendix

DERIVATION OF MAC FOR NITROUS OXIDE

Several articles give values for MAC for a volatile anaesthetic, and for the same volatile agent when mixed with a fixed concentration of nitrous oxide. It now seems clear [41], despite earlier doubts [42, 43], that the current inhaled anaesthetics are additive in their effects. Therefore, it is possible to estimate MAC for nitrous oxide from:

$$\text{MAC}_{\text{N}_2\text{O}} = F\text{E}'_{\text{N}_2\text{O}}/\{(F\text{E}'_{\text{vol2}} - F\text{E}'_{\text{vol1}})/F\text{E}'_{\text{vol2}}\}$$

where $F\text{E}'_{\text{N}_2\text{O}}$ = fixed end-tidal concentration of nitrous oxide, and $F\text{E}'_{\text{vol1}}$ and $F\text{E}'_{\text{vol2}}$ = end-tidal concentrations of volatile agent required to prevent movement in 50% of patients, with and without nitrous oxide, respectively. This has been done here for six studies [3, 4, 28, 31–33]. In three further studies where a volatile anaesthetic was combined with two or more concentrations of nitrous oxide [19, 24, 26], MAC values for both agents can be obtained by extrapolation to zero volatile concentration for nitrous oxide and, where necessary [26], to zero nitrous oxide concentration for the volatile agent.

In studies where only the inspired concentration of nitrous oxide has been reported, the end-tidal concentration has been taken to be 0.97 of the inspired concentration to allow for a theoretical [44] 3% incomplete equilibration of alveolar with 70% inspired nitrous oxide at 20–30 min after the start of administration. Where only the carrier gas concentration has been reported, the inspired concentration has first been estimated by multiplying by $(1 - F_v)$ where F_v = fractional concentration of the volatile agent in the nitrous oxide—volatile mixture.

WEIGHTING OF STUDIES

The best method of combining a number of estimates is to weight each in proportion to the reciprocal of its variance: this leads to a minimum-variance combined estimate [45]. Standard errors, where they are reported in the literature, vary widely and this is likely to be, at least in part, because of the relatively small numbers of patients in any one group and probably to different methods of estimating SE. Therefore, it is assumed here that the variability between patients is inherently a constant, and the same for all inhaled anaesthetics. On this basis, the appropriate weighting of the mean age data can be achieved by making the weight of each estimate of MAC proportional to the number of patients on which it is based.

In the case of nitrous oxide, most estimates of MAC are derived from the difference between MAC values for a volatile in two groups of patients, with and without nitrous oxide (or with two different concentrations of nitrous oxide). The variance of a difference is the sum of the two variances, so the appropriate weighting is $n/2$, where n = number of patients in each group, or $(n_1^{-1} + n_2^{-1})^{-1}$, when the numbers n_1 and n_2 in the two groups are unequal. For each of the two studies [19, 24] which obtained MAC for nitrous oxide in children by extrapolation to zero concentration of the volatile anaesthetic, three differences were involved. Therefore, the variances of each of the resulting estimates of MAC for nitrous oxide can be thought of as each arising from the mean of three differences; therefore the estimates were assigned weights of $3n/2$ (where n = number of patients in each group) as a tolerable approximation for the purpose of the present analyses.

THEORY

It is well known that MAC for inhaled anaesthetics is closely, negatively, correlated with the oil/gas partition coefficient λ [46]. Using the present fitted values of MAC (in percentages) at age 40 yr, and the values of the ratio λ from Halsey [47], leads to a mean value for $\lambda \times$ MAC of 130 with an SD of 28—a coefficient of variation of 20%. Compared with the range of MAC values between different anaesthetics (a ratio of 650 between the largest and smallest) this is small. As many investigators have noted [46], this suggests that the site of action of inhaled anaesthetics is lipid-like.

Assume that for any one of the 12 anaesthetics studied here, the concentration C_s at the site of action (for no movement in response to the surgical incision in 50% of patients) can be represented by

$$C_s = \lambda_s \times \text{MAC}$$

where λ_s = site/gas partition coefficient for that anaesthetic.

Assume also that C_s is the same for all 12 anaesthetics (at any given age) and that, for each anaesthetic, λ_s is independent of age. Then, for any two inhaled anaesthetics i, j, at any two ages a, b,

$$C_{sa} = \lambda_{si} \times \text{MAC}_{ia} = \lambda_{sj} \times \text{MAC}_{ja}$$

and

$$C_{sb} = \lambda_{si} \times \text{MAC}_{ib} = \lambda_{sj} \times \text{MAC}_{jb}$$

Therefore,

$$\frac{\text{MAC}_{ia}}{\text{MAC}_{ib}} = \frac{\text{MAC}_{ja}}{\text{MAC}_{jb}} = \frac{C_{sa}}{C_{sb}}$$

whence

$$\log \text{MAC}_{ia} - \log \text{MAC}_{ib} = \log \text{MAC}_{ja} - \log \text{MAC}_{jb} = \log C_{sa} - \log C_{sb}$$

that is the decrease in logMAC from age a to age b is the same for anaesthetics i and j, and therefore for all 12 anaesthetics.

Thus the current finding of a common slope of log MAC on age for all 12 anaesthetics is to be expected if the concentration required at the site of action is the same for all anaesthetics and if each λ_s is independent of age. The mathematics can readily be extended to include the case of λ_s being dependent on age but with $\log \lambda_s$ having the same slope on age for all 12 anaesthetics.

The above argument is a long way from proving that the variation of MAC with age should be the same for all anaesthetics, but it does show that the present result is not surprising.

References

1. Eger EI II. *Anesthetic Uptake and Action.* Baltimore: Williams and Wilkins, 1974; 1–3.
2. Munson ES, Hoffman JC, Eger EI II. Use of cyclopropane to test generality of anesthetic requirement in the elderly. *Anesthesia and Analgesia* 1984; **63**: 998–1000.
3. Rampil IJ, Lockhart SH, Zwass MS, Peterson N, Yasuda N, Eger EI II, Weiskopf RB, Damask MC. Clinical characteristics of desflurane in surgical patients: minimum alveolar concentration. *Anesthesiology* 1991; **74**: 429–433.
4. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI II, Miller RD, deJong RH, Elashoff RM. Minimum alveolar concentration (MAC) of isoflurane with and without nitrous oxide in patients of various ages. *Anesthesiology* 1975; **42**: 197–200.
5. Nakajima R, Nakajima Y, Ikeda K. Minimum alveolar concentration of sevoflurane in elderly patients. *British Journal of Anaesthesia* 1993; **70**: 273–275.
6. Da Silva JMC. *Closed System Anaesthesia* (PhD Thesis). Cardiff: University of Wales College of Medicine, 1990; 134.
7. Andersen B. *Methodological Errors in Medical Research.* Oxford: Blackwell, 1990; 39.
8. Taguchi M, Watanabe S, Asakura N, Inomata S. End-tidal sevoflurane concentrations for laryngeal mask airway insertion and for tracheal intubation in children. *Anesthesiology* 1994; **81**: 628–631.
9. Nicodemus HF, Nassiri-Rahimi C, Bachman L, Smith TC. Median effective doses (ED50) of halothane in adults and children. *Anesthesiology* 1969; **31**: 344–348.
10. Inomata S, Watanabe S, Taguchi M, Okada M. End-tidal sevoflurane concentration for tracheal intubation and minimum alveolar concentration in pediatric patients. *Anesthesiology* 1994; **80**: 93–96.
11. Kimura T, Watanabe S, Asakura N, Inomata S, Okada M, Taguchi M. Determination of end-tidal sevoflurane concentration for tracheal intubation and minimum alveolar anesthetic concentration in adults. *Anesthesia and Analgesia* 1994; **79**: 378–381.
12. Zbinden AM, Maggiorini M, Petersen-Felix S, Lauber R, Thomson DA, Minder CE. Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. *Anesthesiology* 1994; **80**: 253–260.
13. Saidman LJ, Eger EI II, Munson ES, Babad AA, Muallem M. Minimum alveolar concentration of methoxyflurane, halothane, ether and cyclopropane in man: correlation with theories of anesthesia. *Anesthesiology* 1967; **28**: 994–1002.
14. Gregory GA, Eger EI II, Munson ES. The relationship between age and halothane requirement in man. *Anesthesiology* 1969; **30**: 488–491.
15. Bridges BE jr, Eger EI II. The effect of hypocapnia on the level of halothane anesthesia in man. *Anesthesiology* 1966; **27**: 634–637.
16. Forbes AR, Cohen NH, Eger EI II. Pancuronium reduces halothane requirement in man. *Anesthesia and Analgesia* 1979; **58**: 497–499.
17. Lerman J, Robinson S, Willis MM, Gregory GA. Anesthetic requirements for halothane in young children 0–1 month and 1–6 months of age. *Anesthesiology* 1983; **59**: 421–424.
18. Miller RD, Wahrenbrock EA, Schroeder CF, Knipstein TW, Eger EI II, Buechel DR. Ethylene–halothane anesthesia: addition or synergism? *Anesthesiology* 1969; **31**: 301–304.
19. Murray DJ, Mehta MP, Forbes RB, Dull DL. Additive contribution of nitrous oxide to halothane MAC in infants and children. *Anesthesia and Analgesia* 1990; **71**: 120–124.
20. Cameron CB, Robinson S, Gregory GA. The minimum anesthetic concentration of isoflurane in children. *Anesthesia and Analgesia* 1984; **63**: 418–420.
21. McEwan AI, Smith C, Dyar O, Goodman D, Smith LR, Glass PSA. Isoflurane minimum alveolar concentration; reduction by fentanyl. *Anesthesiology* 1993; **78**: 864–869.
22. Mather C, Raftery S, Prys-Roberts C. Somatic movement and oesophageal motility during isoflurane anaesthesia. *British Journal of Anaesthesia* 1992; **69**: 40–44.
23. LeDez KM, Lerman J. The minimum alveolar concentration (MAC) of isoflurane in preterm neonates. *Anesthesiology* 1987; **67**: 301–307.
24. Murray DJ, Mehta MP, Forbes RB. The additive con-

tribution of nitrous oxide to isoflurane MAC in infants and children. *Anesthesiology* 1991; **75**: 186–190.

25. Gion H, Saidman LJ. The minimum alveolar concentration of enflurane in man. *Anesthesiology* 1971; **35**: 361–364.
26. Torri G, Damia G, Fabiani ML. Effect of nitrous oxide on the anaesthetic requirement of enflurane. *British Journal of Anaesthesia* 1974; **46**: 468–472.
27. Katoh T, Ikeda K. Minimum alveolar concentration of sevoflurane in children. *British Journal of Anaesthesia* 1992; **68**: 139–141.
28. Katoh T, Ikeda K. The minimum alveolar concentration (MAC) of sevoflurane in humans. *Anesthesiology* 1987; **66**: 301–303.
29. Scheller MS, Saidman LJ, Partridge BL. MAC of sevoflurane in humans and the New Zealand white rabbit. *Canadian Journal of Anaesthesia* 1988; **35**: 153–156.
30. Nagayama T, Meguro K, Inada Y. Sevoflurane MAC in the elderly. *Japanese Journal of Anesthesiology* 1994; **43**: 238–241.
31. Lerman J, Sikich N, Kleinman S, Yentis S. The pharmacology of sevoflurane in infants and children. *Anesthesiology* 1994; **80**: 814–824.
32. Munson ES, Saidman LJ, Eger EI II. Effect of nitrous oxide and morphine on the minimum anesthetic concentration of fluroxene. *Anesthesiology* 1965; **26**: 134–139.
33. Gold MI, Abello D, Herrington C. Minimum alveolar concentration of desflurane in patients older than 65 yr. *Anesthesiology* 1993; **79**: 710–714.
34. Taylor RH, Lerman J. Minimum alveolar concentration of desflurane and hemodynamic responses in neonates, infants, and children. *Anesthesiology* 1991; **75**: 975–979.
35. Cullen SC, Eger EI II, Cullen BF, Gregory P. Observations on the anesthetic effect of the combination of xenon and halothane. *Anesthesiology* 1969; **31**: 305–309.
36. Hornbein TF, Eger EI II, Winter PM, Smith G, Wetstone D, Smith KH. The minimum alveolar concentration of nitrous oxide in man. *Anesthesia and Analgesia* 1982; **61**: 553–556.
37. Armitage P, Berry G. *Statistical Methods in Medical Research*, 3rd Edn. London: Blackwells, 1994; 215–219.
38. Healey MJR. *GLIM: an Introduction.* Oxford: Clarendon Press, 1988.
39. Francis B, Green M, Payne C, eds. *The GLIM System—Release 4 Manual.* Oxford: Clarendon Press, 1993.
40. Stewart LA, Parmar MKB. Meta-analysis of the literature or of individual patient data: is there a difference? *Lancet* 1993; **341**: 418–422.
41. Gonowski CT, Eger EI II. Nitrous oxide minimum alveolar anesthetic concentration in rats is greater than previously reported. *Anesthesia and Analgesia* 1994; **79**: 710–712.
42. Eger EI. Does 1 + 1 = 2? *Anesthesia and Analgesia* 1989; **68**: 551–555.
43. Cole DJ, Kalichman MW, Shapiro HM, Eger EI II. Does 1 + 1 = 2?—A continuing debate. *Anesthesia and Analgesia* 1990; **70**: 126–127.
44. Mapleson WW. Pharmacokinetics of inhaled anaesthetics. In: Nunn JF, Utting JE, Brown BR jr, eds. *General Anaesthesia*, 5th Edn. London: Butterworths, 1989; 44–59.
45. Davies OL, Goldsmith PL, eds. *Statistical Methods in Research and Production*, 4th Edn. London: Longmans, 1972; 161–162, 236.
46. Halsey MJ. Molecular mechanisms of anaesthesia. In: Nunn JF, Utting JE, Brown BR jr, eds. *General Anaesthesia*, 5th Edn. London: Butterworths, 1989; 19–29.
47. Halsey MJ. Potency and physical properties of inhalational anaesthetics. In: Nunn JF, Utting JE, Brown BR jr, eds. *General Anaesthesia*, 5th Edn. London: Butterworths, 1989; 7–18.

British Journal of Anaesthesia 1996; **76**: 186–193

Omitting nitrous oxide in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials

M. TRAMÈR, A. MOORE AND H. MCQUAY

Summary

We have reviewed randomized controlled trials to assess the effectiveness and safety of anaesthetics which omitted nitrous oxide (N_2O) to prevent postoperative nausea and vomiting (PONV). Early and late PONV (6 and 48 h after operation, respectively), and adverse effects were evaluated using the numbers-needed-to-treat (NNT) method. In 24 reports with information on 2478 patients, the mean incidence of early and late vomiting with N_2O (control) was 17% and 30%, respectively. Omitting N_2O significantly reduced vomiting compared with a N_2O regimen; the combined NNT to prevent both early and late vomiting with a N_2O-free regimen was about 13 (95% confidence intervals (CI) 9, 30). The magnitude of the effect depended on the incidence of vomiting in controls. In studies with a baseline risk higher than the mean of all reports, the NNT to prevent both early and late vomiting with a N_2O-free anaesthetic was 5 (95% CI 4, 10). When the baseline risk was lower than the mean, omitting N_2O did not improve outcome. Omitting N_2O had no effect on complete control of emesis or nausea. The NNT for intraoperative awareness with a N_2O-free anaesthetic was 46 compared with anaesthetics where N_2O was used. This clinically important risk of major harm reduces the usefulness of omitting N_2O to prevent postoperative emesis. (*Br. J. Anaesth.* 1996; **76**: 186–193)

Key words

Anaesthetics gases, nitrous oxide. Vomiting, nausea. Memory. Vomiting, nausea, anaesthetic factors. Anaesthesia, audit. Anaesthesia, depth.

Theoretically, nitrous oxide (N_2O) is an emetic and it is generally believed to be associated with postoperative nausea and vomiting (PONV). N_2O penetrates easily into closed spaces such as the bowel [1, 2] or middle ear [3–5], activates the medullary dopaminergic system [6] and increases cerebrospinal opioid peptides [7]. In humans, N_2O analgesia was shown to be reversible by naloxone [8]. These data suggest that N_2O could induce PONV through at least three mechanisms and experimental studies with N_2O reported nausea and vomiting in healthy volunteers [9–11].

The effect of N_2O on the incidence of PONV is controversial [12]. Palazzo and Strunin classified N_2O as an agent known to cause PONV, claiming that the most likely mechanism was gastrointestinal distension by manual ventilation and N_2O transfer to the gastrointestinal tract [13]. Others questioned a decrease in the incidence of PONV when N_2O was omitted in halogenated inhalation anaesthetics, but suggested that omitting N_2O in propofol anaesthesia may be beneficial [14].

This meta-analysis of randomized controlled trials (RCT) tested the evidence that general anaesthetics which omit N_2O are associated with a decreased incidence of PONV. Statistical and clinical significance of the effect of N_2O-free anaesthetics on PONV compared with regimens including N_2O, and anaesthesia-related complications were evaluated using odds ratio and number-needed-to-treat (NNT) methods.

Methods

Medline was searched (1966 to May 1995) without language restriction for RCT which evaluated the effect on PONV of a N_2O-free anaesthetic (treatment) compared with the same anaesthetic but including N_2O (control). Key words used were "nitrous oxide" and "vomiting" or "nausea". Additional reports were identified from the reference lists of retrieved trials and from review articles of PONV. Unpublished studies were not sought. Each published report which could possibly be described as an RCT was read independently by each of the authors, who scored the reports for quality using a three item scale [15] and then met to agree consensus scores. All RCT reporting emetic outcome as dichotomous data were included. Studies without randomization and abstracts were not considered.

Information on patient characteristics, surgery, anaesthetics, definition of emesis and adverse effects was obtained from each report. Dichotomous data of the incidence of early PONV (up to 6 h after operation) and late PONV (up to 48 h after operation) were extracted. When several incidences of PONV were reported at different times (time intervals, for instance [16]) the two cumulative values nearest to 6 h and 48 h after operation were analysed. Effectiveness was defined as absence of emesis. Complete control of emesis was analysed when

---

MARTIN TRAMÈR, MD, ANDREW MOORE, DPHIL, HENRY MCQUAY, DM, Pain Research, Nuffield Department of Anaesthetics, Churchill Hospital, Headington, Oxford OX3 7LJ. Accepted for publication: September 19, 1995;

Correspondence to M.T.

mentioned specifically in the reports (number of patients without any emetic symptoms, for instance). The incidence of nausea and vomiting was analysed separately when reported. Retching, when reported as a separate outcome, was added to the incidence of vomiting. No weighting was used for different grades of nausea, number of vomiting episodes, time to first vomiting episode, number of patients needing antiemetic rescue therapy or delay until discharge. The incidence of intraoperative awareness was recorded as indicated in the reports.

Odds ratios (OR) with 95 % confidence intervals (95 % CI) were calculated using a fixed effects model. NNT and 95 % CI were calculated [17]. This was done for effectiveness and adverse effects, both for individual reports and by combining single treatment or control arms. A statistically significant improvement in a N_2O-free regimen compared with control was assumed when the lower limit of the 95 % CI of the OR was > 1. In the text, NNT for effectiveness and adverse effects are reported with 95 % CI only when the OR indicated a statistically significant improvement in the treatment compared with control. Point estimates of the NNT without 95 % CI are reported when the OR was not statistically significant. An infinite value for NNT indicates a negative value. Calculations were performed using Excel v 4.0 on a Macintosh IIci.

Results

REPORTS

We identified 32 publications. Our search strategy detected 17 reports from Medline. Eight trials were excluded; one was not randomized [18], five had an inadequate randomization method (alternate allocation [19]; patient's date of birth [16, 20, 21]; patient's registration number [22]), and in two the emetic outcome was not reported as dichotomous data [23, 24]. One RCT without dichotomous PONV data was included in the awareness analysis because recall was an outcome [25].

The 24 analysed reports contained data on 2478 patients. N_2O and PONV interactions were evaluated with isoflurane (eight trials), enflurane (three), halothane (three), desflurane (five) and propofol (six). In the three largest RCT, more than 680 patients had a N_2O-free anaesthetic with either isoflurane [26, 27], enflurane [26] or halothane [28]. In three studies, about 50 treated patients were analysed in each treatment arm [29–31]. In each of the remaining 18 studies, N_2O and PONV interactions were investigated in no more than 35 patients who had a N_2O-free anaesthetic [1, 25, 32–47]. Tables containing information extracted from all trials are available from the authors.

OUTCOMES

Complete control of emesis with no emetic symptoms in the postoperative period was reported in four studies. In two studies, this was the only emetic outcome [36, 45]. For both early and late complete emetic control, there was no significant improvement in N_2O-free techniques compared with control (table 1).

Nausea as a separate outcome was reported in 14 studies. In one study this was the only emetic outcome [1]. Omitting N_2O had no impact on early or late postoperative nausea (table 1).

The incidence of vomiting, with or without retching, was reported in 19 studies. In four studies this was the only emetic outcome [27, 28, 37, 46]. For early and late times, the mean incidence of vomiting in controls was 17 % and 30 %, respectively. For early vomiting, anaesthetics which omitted N_2O produced statistically significant improvement over control and the combined NNT to prevent early vomiting was 11.8 (8.5, 19.4) (table 1). For late vomiting, N_2O-free regimens also produced a statistically significant improvement over control, and the combined NNT to prevent late vomiting was 13.8 (8.8, 31.6) (table 1).

EFFECT OF BASELINE RISK ON OUTCOME

All three large studies reported vomiting as a separate outcome [26–28]. In two the incidence of vomiting in controls was less than 10 % for early and only 13.3–28.7 % for late vomiting [26, 28]. NNT point estimates were 29 and 105 to prevent early vomiting and 30 and 305 to prevent late vomiting. The third reported a high baseline risk for late vomiting in controls (46 %) and the NNT point estimate to prevent vomiting with a N_2O-free regimen was 8.5 [27].

When all trials reporting vomiting as an outcome were analysed baseline risks of vomiting and corresponding NNT to prevent vomiting by omitting N_2O showed an inverse relationship (figs 1, 2). Combined analysis of trials with a baseline risk lower than the mean of all trials showed no improvement in the N_2O-free groups over controls (tables 2, 3). In this subgroup, the mean baseline risk was very low; 7 % (range 0–13 %) for early and 20 % (0–29 %) for late vomiting. Combined analysis of trials with a baseline risk higher than the mean showed statistically significant improvement of the N_2O-free regimens over control (tables 2, 3). In this subgroup, the mean baseline risk was high; 35 % (21–50 %) for early and 51 % (43–71 %) for late vomiting, and the NNT to prevent early and late vomiting with a N_2O-free technique were 4.8 (95 % CI 3.6, 7.3) and 5.6 (3.9, 10.1), respectively. Anaesthetic techniques and types of surgery were similar in the subgroups (tables 2, 3).

Subgroups were different from each other in terms of risk reductions and NNT to prevent vomiting with a N_2O-free technique (tables 2, 3). For early vomiting the risk reduction was twice, and for late vomiting it was three times higher in studies with a high baseline risk of vomiting compared with those with a low risk (tables 2, 3). The corresponding NNT to prevent vomiting with a N_2O-free technique were 8–12-fold different.

When the three large studies [26–28] were excluded from the subgroup analysis the inverse relationship between incidence of vomiting in controls and corresponding NNT to prevent vomiting

Table 1 Odds ratio and numbers-needed-to-treat (NNT) to prevent early and late postoperative emesis by omitting nitrous oxide. ∞ = Infinite value

	Absence of emesis on air–O_2	Absence of emesis on N_2O	Odds ratio (95% CI)	NNT (95% CI)	Reference
Early complete emetic control	363/417	352/409	1.1 (0.7, 1.6)	101 (17.7, ∞)	[26, 45]
Late complete emetic control	269/416	247/398	1.1 (0.8, 1.5)	38.4 (10.8, ∞)	[26, 36, 44]
Prevention of early nausea	524/610	502/608	1.3 (0.9, 1.8)	30 (13.5, ∞)	[1, 26, 32, 34, 35, 40, 41, 43, 44, 47]
Prevention of late nausea	359/526	329/502	1.1 (0.9, 1.5)	36.9 (11.8, ∞)	[26, 29, 30, 33, 35, 39]
Prevention of early vomiting	689/749	619/741	2.4 (1.7, 3.3)	11.8 (8.5, 19.4)	[26, 30–32, 34, 35, 37, 38, 40–43, 46, 47]
Prevention of late vomiting	700/907	609/871	1.5 (1.2, 1.8)	13.8 (8.8, 31.6)	[26–30, 33, 35, 38, 39, 42, 46]

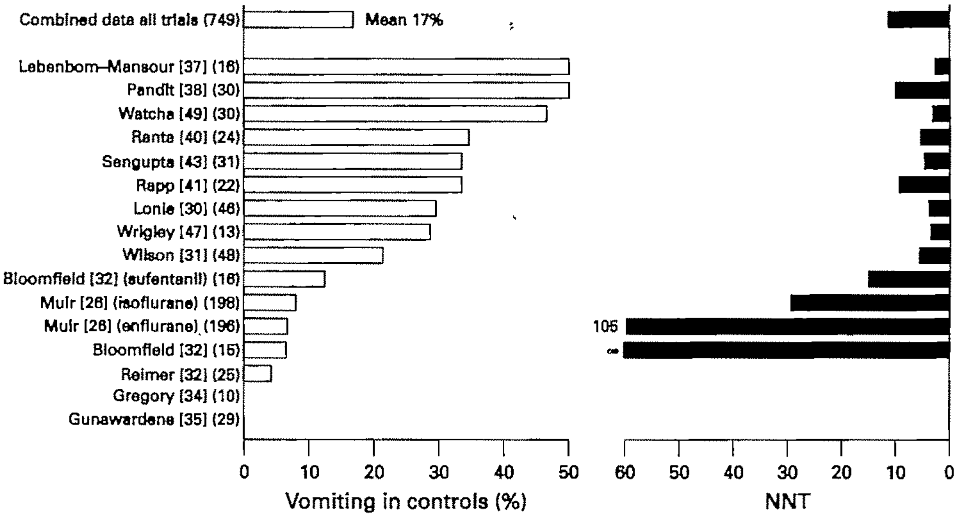


Figure 1 Incidence of early vomiting in controls (baseline risk) and corresponding numbers-needed-to-treat (NNT) to prevent early vomiting by omitting nitrous oxide. [Numbers in square brackets are reference numbers.] (Numbers in parentheses indicate the number of patients in the nitrous oxide-free group.) ∞ = Infinite value.

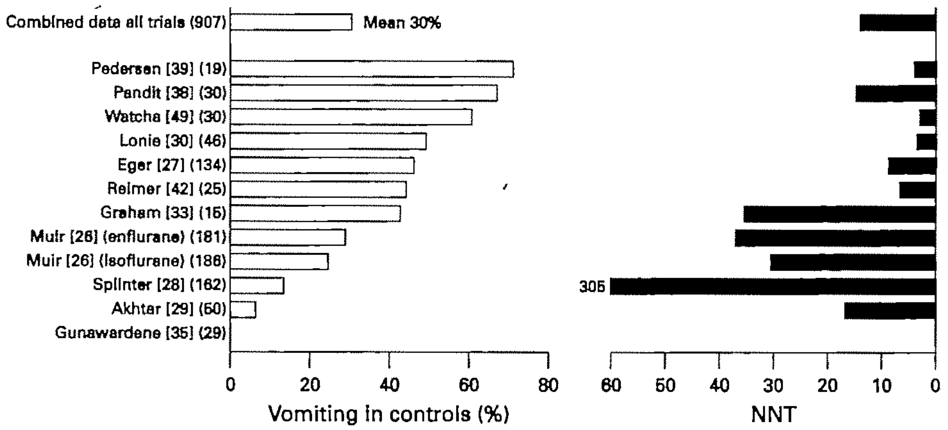


Figure 2 Incidence of late vomiting in controls (baseline risk) and corresponding numbers-needed-to-treat (NNT) to prevent late vomiting by omitting nitrous oxide. [Numbers in square brackets are reference numbers.] (Numbers in parentheses indicate the number of patients in the nitrous oxide-free groups.)

with a N_2O-free anaesthetic was maintained (tables 2, 3).

PROPOFOL

The incidence of vomiting was analysed separately in five studies investigating N_2O and propofol interactions [29, 35, 34, 42, 46]. For both early and late vomiting, a total i.v. anaesthetic (TIVA) with propofol led to a statistically significant improvement compared with a propofol–N_2O regimen (lower 95% CI of the OR 1.1 for early and 1.4 for late vomiting, respectively). The NNT to prevent early vomiting with a propofol-based TIVA was 10.4 (5.4, 149) in four studies with 94 treated patients [34, 35, 42, 46]. The NNT to prevent late vomiting was 7.4 (4.5, 22) in four studies with 134 treated patients [29, 35, 42, 46]. Only one study reported statistically significant improvement in the N_2O-free propofol anaesthetic compared with control for both early and late vomiting [46]. Another study reported statistically significant improvement in the N_2O-free regimen for late but not for early vomiting [42]. In both reports the incidence of vomiting in controls was high; 47% for early and 44–60% for late vomiting [42, 46].

Table 2 Baseline risk, risk reduction, and numbers-needed-to-treat (NNT) to prevent early vomiting by omitting nitrous oxide. ∞ = Infinite value. Def. = Definition; PONV = postoperative nausea and vomiting; V = vomiting; R = retching; N_2O = nitrous oxide; Extra-abd = extra-abdominal; Abd = abdominal; Gyn = gynaecological; Uro = urological; Laps = laparoscopy; diff = different operations; Paed strab = paediatric strabismus surgery; Paed tons = paediatric tonsillectomies; Ortho = orthopaedic operations; ENT = ear, nose and throat

Ref.	Surgery	Main anaesthetic	Mode of ventilation	Opioid use	Gastric suction	Duration of intervention (mean) an = anaesthetic	Def. of PONV	%PONV N_2O (control)	%PONV air–O_2 (active)	Risk reduction (%)	Odds ratio (95% CI)	NNT (95% CI)
Studies with low baseline risk (< 17%)												
[32]	Extra-abd	Isoflurane	Intubation	No	Yes	> 30 min (an)	V	13%	6%	50%	2.0 (0.2, 21.2)	16 (3.8, ∞)
[32]	Extra-abd	Isoflurane	Intubation	Yes	Yes	> 30 min (an)	V	6%	13%	−113%	0.5 (0.04, 4.7)	∞
[34]	Gyn major	Propofol	Intubation	Yes	No	30–68 min	V	0%	0%	0%	0	0
[35]	Gyn minor	Propofol	Mask	No	No	5–10 min	V	0%	0%	0%	0	0
[26]	Adults diff	Enflurane	Intubation	Yes	No	80 min (an)	R+V	7%	6%	15%	1.2 (0.5, 2.7)	104.9 (17.6, ∞)
[26]	Adults diff	Isoflurane	Intubation	Yes	No	80 min (an)	R+V	8%	5%	43%	1.8 (0.8, 4.1)	29.1 (12.1, ∞)
[42]	Paed strab	Propofol	Intubation	Yes	No	29 min	R+V	4%	4%	0%	1.0 (0.1, 16.5)	0 (9.2, ∞)
Combined data								**7%**	**5%**	**27%**	**1.4 (0.8, 2.4)**	**57.8 (21.4, ∞)**
Combined data without large trials ([26–28])											1.0 (0.2, 4.1)	∞
Studies with high baseline risk (> 17%)												
[37]	Ortho minor	Desflurane	Intubation	Yes	No	94 min (an)	V	50%	13%	75%	5.6 (1.2, 26.2)	2.7 (1.5, 14.9)
[30]	Gyn laps	Enflurane	Intubation	Yes	No	40 min (an)	V	29%	4%	85%	6.2 (2, 19.4)	4.0 (2.5, 10.2)
[38]	Paed tons	Halothane	Intubation	Yes	Yes	37 min	R+V	50%	40%	20%	1.5 (0.5, 4.1)	10 (2.9, ∞)
[40]	Abd major	Isoflurane	Intubation	Yes	Yes	121 min (an)	R+V	35%	17%	52%	2.5 (0.7, 8.7)	5.6 (2.4, ∞)
[41]	Ortho minor	Desflurane	Intubation	Yes	No	57 min	V	33%	23%	32%	1.7 (0.5, 6.0)	9.4 (2.8, ∞)
[43]	Laps	Enflurane	Intubation	Yes	No	15 min	V	33%	13%	61%	3.1 (0.97, 9.7)	4.9 (2.5, ∞)
[46]	Paed strab	Propofol	Intubation	Yes	Yes	54 min	V	47%	17%	64%	3.9 (1.3, 11.5)	3.3 (1.9, 13)
[31]	Paed ENT	Halothane	Mask	No	No	10 min (an)	R+V	21%	4%	80%	4.6 (1.4, 15.5)	5.8 (3.3, 24.3)
[47]	Ortho minor	Desflurane	Intubation	Yes	No	29 min	V	29%	0%	100%	8.9 (1.1, 71.2)	3.5 (1.9, 20.4)
Combined data								**35%**	**14%**	**60%**	**3.1 (2.1, 4.6)**	**4.8 (3.6, 7.3)**
Combined data without large trials ([26–28])											3.1 (2.1, 4.6)	4.8 (3.6, 7.3)

Table 3 Baseline risk, risk reduction and numbers-needed-to-treat (NNT) to prevent late vomiting by omitting nitrous oxide. ∞ = Infinite value. (Abbreviations as in table 2)

Ref.	Surgery	Main anaesthetic	Mode of ventilation	Opioid use	Gastric suction	Duration of intervention (mean) an = anaesthetic	Def. of PONV	%PONV N_2O (control)	%PONV air–O_2 (active)	Risk reduction (%)	Odds ratio (95% CI)	NNT (95% CI)
Studies with low baseline risk (< 30%)												
[29]	Gyn+Uro	Propofol	Mask	No	No	12 min (an)	V	6%	0%	100%	7.7 (0.8, 75.8)	16.7 (8, ∞)
[35]	Gyn minor	Propofol	Mask	No	No	5–10 min	V	0%	0%	0%	0	0
[26]	Adults diff	Enflurane	Intubation	Yes	No	80 min (an)	R+V	29%	26%	9%	1.1 (0.7, 1.8)	37.3 (8.4, ∞)
[26]	Adults diff	Isoflurane	Intubation	Yes	No	80 min (an)	R+V	24%	21%	14%	1.2 (0.7, 2)	30.2 (8.4, ∞)
[28]	Paed ENT	Halothane	Mask	No	No	12 min (an)	V	13%	13%	2%	1 (0.5, 2)	304.7 (13, ∞)
Combined data								**20%**	**18%**	**12%**	**1.2 (0.9, 1.6)**	**43.5 (14.9, ∞)**
Combined data without large trials ([26–28])											7.7 (0.8, 75.8)	26.3 (12.5, ∞)
Studies with high baseline risk (> 30%)												
[27]	Adults diff	Isoflurane	Intubation	Yes	No	178 min (an)	V	46%	34%	25%	1.6 (1, 2.7)	8.5 (4.3, ∞)
[33]	Gyn laps	Desflurane	Intubation	Yes	No	25 min (an)	V	43%	40%	7%	1.1 (0.3, 4.8)	35 (2.6, ∞)
[30]	Gyn laps	Enflurane	Intubation	Yes	No	40 min (an)	V	49%	17%	64%	4.1 (1.7, 10.2)	3.2 (2, 8)
[38]	Paed tons	Halothane	Intubation	Yes	Yes	37 min	R+V	67%	60%	10%	1.3 (0.5, 3.8)	15 (3.3, ∞)
[39]	Gyn major	Isoflurane	Intubation	Yes	No	99 min	V	71%	42%	40%	3.1 (0.8, 11.3)	3.5 (1.7, ∞)
[42]	Paed strab	Propofol	Intubation	Yes	No	29 min	R+V	44%	28%	36%	2 (0.6, 6.2)	6.3 (2.4, ∞)
[46]	Paed strab	Propofol	Intubation	Yes	Yes	54 min	V	60%	23%	61%	4.4 (1.6, 12.2)	2.7 (1.7, 7.4)
Combined data								**51%**	**33%**	**35%**	**2.1 (1.5, 2.9)**	**5.6 (3.9, 10.1)**
Combined data without large trials ([26–28])											2.7 (1.7, 4.3)	4.1 (2.8, 7.4)

INTRAOPERATIVE AWARENESS

One RCT reported intraoperative awareness in six of 134 patients in the N_2O-free group and in one of 126 in the control group [27]. Patients in this study were premedicated with triazolam. In one study without premedication, one incidence of recall was reported in 31 patients in the N_2O-free group [43]. Five studies reported explicitly the absence of intraoperative awareness in the N_2O-free groups [25, 30, 34, 36, 47]. The NNT for one patient experiencing intraoperative awareness with a N_2O-free anaesthetic compared with a regimen with N_2O was 46.2 (24.1, 581); the odds ratio was 4.5 (1.1, 18).

Discussion

The controversy on the effect of N_2O on PONV [48, 49] may result from three problems. First, most data from N_2O and PONV interactions are based on small studies and some showed statistically significant improvement with N_2O-free regimens [30, 31, 37, 46, 47] whereas large studies involving hundreds of patients did not show any difference [22, 26, 28]. Second, pharmacological antiemetic effectiveness can be reported as absence of nausea, of vomiting with or without retching, or of any emetic event (i.e. complete emetic control). Some studies reported only one of these outcomes. However, the effect of N_2O on these emetic outcomes was shown to be different. Finally, the confusion about N_2O and PONV interactions may simply reflect general difficulty in interpreting the clinical significance of the effectiveness of a N_2O-free regimen in preventing PONV.

This meta-analysis overcame these problems by combining results from all relevant reports, by recording each emetic outcome separately and by analysing both the statistical and clinical significance of the effect of a N_2O-free anaesthetic on PONV. Omitting N_2O in general anaesthesia had no effect on the incidence of nausea or on complete emetic control; however, it was followed by a statistically significant reduction in early and late vomiting and the NNT indicated that patients at high risk of vomiting were the most likely to profit from omitting N_2O.

The baseline risk of vomiting is of multifactorial origin. Types of surgery, anaesthetic techniques, sex and age of patients were comparable in subgroups with a low or high baseline risk of vomiting. Even in paediatric strabismus surgery, a well defined subgroup with a recognized high baseline risk of postoperative vomiting, an extraordinarily wide range of vomiting incidence has been reported [50]. This suggests that the baseline risk of vomiting is not simply dependent on a particular type of surgery, anaesthetic or patient but is rather defined by the whole clinical setting.

Interestingly, the risk reduction was not useful as a predictor of the emesis-reducing effect of a N_2O-free anaesthetic. For early vomiting, the combined risk reduction with a N_2O-free anaesthetic was 27% in studies with a low baseline incidence of vomiting. However, the NNT method indicated that almost 60 patients would need to be treated with a N_2O-free anaesthetic in this setting for one to profit. For late vomiting the risk reduction with a N_2O-free anaesthetic in studies with a high baseline risk of vomiting was only slightly higher (35%) but this time only six patients needed to undergo a N_2O-free anaesthetic for one to profit. This proves that the NNT is a useful measure of clinical significance because it takes into account the risk both with and without treatment. This also confirms that the NNT method is helpful in identifying a high-response subgroup of patients who have the most to gain from the treatment [51].

Subgroup analysis can be informative but it is also potentially misleading [52]. To omit such pitfalls, we first described a difference in the magnitude of the emesis-preventing effect of a N_2O-free anaesthetic that is clinically important. Second, if a hypothesis is confirmed in a meta-analysis that excludes data from the study that originally suggested a particular interaction, the inference is stronger. Analysis of the largest trials suggested an inverse relationship between baseline risk of vomiting and NNT to prevent vomiting with a N_2O-free anaesthetic. Exclusion of these studies from the combined analysis confirmed or even accentuated the results of the subgroup analysis. Third, the larger the difference between the effect in a particular subgroup and the overall effect, the more plausible it is that the effect is real. Compared with the combined outcome of all RCT (NNT 12–14 to prevent vomiting) the prevention of vomiting efficiency of a N_2O-free regimen was increased almost three-fold when only the subgroup with a high baseline risk was analysed. When only trials with a low baseline risk were analysed, the overall efficiency of a N_2O-free regimen in decreasing vomiting became three times weaker. Finally, this overview of the relevant literature found an interaction between baseline risk of vomiting and N_2O which was present consistently. It has been suggested that such consistency is the best single index as to whether or not the results of a subgroup analysis should be believed [52].

It has been suggested that omitting N_2O in propofol anaesthesia would be followed by a more pronounced decrease in PONV than omitting N_2O in halogenated anaesthetics [49]. A TIVA with propofol was followed by a statistically significant decrease in vomiting compared with control and the combined NNT to prevent early and late vomiting were lower than the combined data of all RCT. However, the two propofol studies reporting statistically significant improvement in the N_2O-free anaesthetic also reported a high incidence of vomiting in controls, supporting the results of the baseline risk subgroup analysis. Moreover, for early vomiting, the confidence interval of the combined NNT was very wide, indicating that this result has to be interpreted cautiously.

The benefit of a particular intervention has to be balanced against its potential for harm. In the most advantageous clinical situation (i.e. a setting with a high risk of PONV), 20% of treated patients may profit from the emesis-reducing effect of a N_2O-free anaesthetic. Based on data from this meta-analysis the risk of intraoperative awareness is 10 times lower in the same setting. In the least advantageous situation (i.e. a setting with a low risk of PONV), for every patient profiting from a N_2O-free anaesthetic one other would experience intraoperative awareness. The question is then if the result of the meta-analysis is representative, as only seven of 24 RCT reported recall as an outcome. The confidence interval of the NNT indicated that we can be 95% confident that intraoperative awareness does occur between in as many as 4% or in as few as 0.17% of patients undergoing a N_2O-free anaesthetic. In a series of 180 consecutive patients undergoing general anaesthesia without N_2O, none reported recall [53]. In this situation we would be 95% confident that the chance of intraoperative awareness with a N_2O-free anaesthetic is at most 1.7% [54]. The result of Moseley and colleagues [53] is in agreement with the result of our meta-analysis and we have to assume that the NNT point estimate from our calculation (NNT 46) lies close to the "true" value. Conscious awareness with recall produced by a particular anaesthetic technique is major harm and indeed is of major concern both to patients and anaesthetists. It can lead to serious psychological sequelae [55, 56]. Premedication with benzodiazepines does not guarantee absence of recall [27], but even in the presence of N_2O, intraoperative awareness may occur [57].

In conclusion, omitting N_2O from general anaesthetics decreases postoperative vomiting significantly but only if the baseline risk of vomiting is high. Omitting N_2O does not affect nausea or complete control of emesis. There is no evidence that omitting N_2O is more effective in propofol than in halogenated anaesthetics. The clinically important risk of intraoperative awareness with a N_2O-free anaesthetic reduces the usefulness of this method of preventing postoperative vomiting.

Acknowledgements

Salary and support for M.T. were provided by the Swiss National Science Foundation and the Swiss Anaesthetic Society. The review was funded by Pain Research Funds.

References

1. Scheinin B, Lindgren L, Scheinin TM. Peroperative nitrous oxide delays bowel function after colonic surgery. *British Journal of Anaesthesia* 1990; **64**: 154–158.
2. Giuffre M, Gross JB. The effects of nitrous oxide on postoperative bowel motility. *Anesthesiology* 1986; **65**: 699–700.
3. Blackstock D, Gettes MA. Negative pressure in the middle ear in children after nitrous oxide anaesthesia. *Canadian Anaesthetists Society Journal* 1986; **33**: 32–35.
4. Davies I, Moore JRM, Lahiri SK. Nitrous oxide and the middle ear. *Anaesthesia* 1979; **34**: 147–151.
5. Montgomery CJ, Vaghadia H, Blackstock D. Negative middle ear pressure and postoperative vomiting in pediatric outpatients. *Anesthesiology* 1988; **68**: 288–291.
6. Murakawa M, Adachi T, Nakao S, Seo N, Shingu K, Mori K. Activation of the cortical and medullary dopaminergic systems by nitrous oxide in rats: a possible neurochemical basis for psychotropic effects and postanesthetic nausea and vomiting. *Anesthesia and Analgesia* 1994; **78**: 376–381.
7. Finck DA, Samaniego E, Ngai SH. Nitrous oxide selectively releases met^5-enkephalin and met^5-enkephalin-arg^6-phe^7 into canine third ventricular cerebrospinal fluid. *Anesthesia and Analgesia* 1995; **80**: 664–670.
8. Yang JC, Clark WC, Ngai SH. Antagonism of nitrous oxide analgesia by naloxone in man. *Anesthesiology* 1980; **52**: 414–417.
9. Brandt L, Pohar H, Gehl A, Neugebauer I. La phase postanaesthésique après inhalation d'halothane, d'enflurane, d'isoflurane et de protoxyde d'azote. *Cahiers d'Anesthésiologie* 1985; **33**: 161–163.
10. Russel GB, Snider MT, Richard RB, Loomis JL. Hyperbaric nitrous oxide as a sole anesthetic agent in humans. *Anesthesia and Analgesia* 1990; **70**: 289–295.
11. Hornbein TF, Eger EI II, Winter PM, Smith G, Wetstone D, Smith KH. The minimum alveolar concentration of nitrous oxide in man. *Anesthesia and Analgesia* 1982; **61**: 553–556.
12. Rabey PG, Smith G. Anaesthetic factors contributing to postoperative nausea and vomiting. *British Journal of Anaesthesia* 1992; **69** (Suppl. 1): 40S–45S.
13. Palazzo MGA, Strunin L. Anaesthesia and emesis II: prevention and management. *Canadian Anaesthetists Society Journal* 1984; **31**: 407–415.
14. Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment, and prevention. *Anesthesiology* 1992; **77**: 162–184.
15. Jadad AR. *Meta-analysis of Randomised Clinical trials in Pain Relief*, thesis. Oxford: Balliol College, 1994; appendix 3.1.
16. Korttila K, Hovorka J, Erkola O. Nitrous oxide does not increase the incidence of nausea and vomiting after isoflurane anesthesia. *Anesthesia and Analgesia* 1987; **66**: 761–765.
17. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *British Medical Journal* 1995; **310**: 452–454.
18. Smiley BAS, Paradise NF. Does the duration of N_2O administration affect postoperative nausea and vomiting? *Nurse Anesthesia* 1991; **2**: 13–18.
19. Lind B, Roland P. Kurznarkosen mit Propanidid. Wie hoch sind die Brechreizfrequenzen? *Der Anaesthesist* 1969; **18**: 82–85.
20. Hovorka J, Korttila K, Erkola O. Nitrous oxide does not increase nausea and vomiting following gynaecological laparoscopy. *Canadian Journal of Anaesthesia* 1989; **36**: 145–148.
21. Melnick BM, Johnson LS. Effects of eliminating nitrous oxide in outpatient anesthesia. *Anesthesiology* 1987; **67**: 982–984.
22. Felts JA, Poler SM, Spitznagel EL. Nitrous oxide, nausea, and vomiting after outpatient gynecologic surgery. *Journal of Clinical Anesthesia* 1990; **2**: 168–171.
23. Lindekaer A, Skielboe M, Guldager H, Jensen EW. The influence of nitrous oxide on propofol dosage and recovery after total intravenous anaesthesia for day-case surgery. *Anaesthesia* 1995; **50**: 397–399.
24. Taylor E, Feinstein R, White PF, Soper N. Anesthesia for laparoscopic cholecystectomy. Is nitrous oxide contraindicated? *Anesthesiology* 1992; **76**: 541–543.
25. Girardi G, Rossi R, Cellai MP, Pieraccioli E, Novelli GP. Anestesia con isoflurano in aria e con isoflurano e protossido di azoto. *Minerva Anestesiologica* 1994; **60**: 321–328.
26. Muir JJ, Warner MA, Offord KP, Buck CF, Harper JV, Kunkel SE. Role of nitrous oxide and other factors in postoperative nausea and vomiting: a randomized and blinded prospective study. *Anesthesiology* 1987; **66**: 513–518.
27. Eger EI II, Lampe GH, Wauk LZ, Whitendale P, Cahalan MK, Donegan JH. Clinical pharmacology of nitrous oxide: an argument for its continued use. *Anesthesia and Analgesia* 1990; **71**: 575–585.
28. Splinter WM, Roberts DJ, Rhine EJ, MacNeill HB, Komocar L. Nitrous oxide does not increase vomiting in children after myringotomy. *Canadian Journal of Anaesthesia* 1995; **42**: 274–276.
29. Akhtar TM, Kerr WJ, Kenny GNC. Effect of nitrous oxide on post-operative nausea and vomiting during propofol anaesthesia for short surgical operations. *European Journal of Anaesthesiology* 1993; **10**: 337–341.
30. Lonie DS, Harper NJN. Nitrous oxide anaesthesia and vomiting. The effect of nitrous oxide anaesthesia on the incidence of vomiting following gynaecological laparoscopy. *Anaesthesia* 1986; **41**: 703–707.
31. Wilson IG, Fell D. Nitrous oxide and postoperative vomiting in children undergoing myringotomy as a day case. *Paediatric Anaesthesia* 1993; **3**: 283–285.
32. Bloomfield E, Hilberman M, Brown P, Noe H, Gaydos J,

Miller G, Sherrill D, Williams G. Postoperative nausea and vomiting. A comparison of sufentanil, nitrous oxide, and isoflurane. *Cleveland Clinical Journal of Medicine* 1988; **55**: 549–552.

33. Graham SG, Aitkenhead AR. A comparison between propofol and desflurane anaesthesia for minor gynaecological laparoscopic surgery. *Anaesthesia* 1993; **48**: 471–475.
34. Gregory MA, Gin T, Yau G, Leung RKW, Chan K, Oh TE. Propofol infusion anaesthesia for Caesarean section. *Canadian Journal of Anaesthesia* 1990; **37**: 514–520.
35. Gunawardene RD, White DC. Propofol and emesis. *Anaesthesia* 1988; 43 (Suppl.): 65–67.
36. Lampe GH, Wauk LZ, Donegan JH, Pitts LH, Jackler RK, Litt LL, Rampil IJ, Eger EI II. Effect on outcome of prolonged exposure of patients to nitrous oxide. *Anesthesia and Analgesia* 1990; **71**: 586–590.
37. Lebenbom-Mansour MH, Pandit SK, Kothary SP, Randel GI, Levy L. Desflurane versus propofol anesthesia: a comparative analysis in outpatients. *Anesthesia and Analgesia* 1993; **76**: 936–941.
38. Pandit UA, Malviya S, Lewis IH. Vomiting after outpatient tonsillectomy and adenoidectomy in children: the role of nitrous oxide. *Anesthesia and Analgesia* 1995; **80**: 230–233.
39. Pedersen FM, Wilken-Jensen C, Knudsen F, Lindekaer AL, Svare EI. The influence of nitrous oxide on recovery of bowel function after abdominal hysterectomy. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 692–696.
40. Ranta P, Nuutinen L, Laitinen J. The role of nitrous oxide in postoperative nausea and recovery in patients undergoing upper abdominal surgery. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 339–341.
41. Rapp SE, Conahan TJ, Pavlin DJ, Levy WJ, Hautman B, Lecky J, Luke J, Nessly ML. Comparison of desflurane with propofol in outpatients undergoing peripheral orthopedic surgery. *Anesthesia and Analgesia* 1992; **75**: 572–579.
42. Reimer EJ, Montgomery CJ, Bevan JC, Merrick PM, Blackstock D, Popovic V. Propofol anaesthesia reduces early postoperative emesis after paediatric strabismus surgery. *Canadian Journal of Anaesthesia* 1993; **40**: 927–933.
43. Sengupta P, Plantevin OM. Nitrous oxide and day-case laparoscopy: effects on nausea, vomiting and return to normal activity. *British Journal of Anaesthesia* 1988; **60**: 570–573.
44. Sukhani R, Lurie J, Jabamoni R. Propofol for ambulatory gynecologic laparoscopy: does omission of nitrous oxide alter postoperative emetic sequelae and recovery? *Anesthesia and Analgesia* 1994; **78**: 831–835.
45. Van Hemelrijck J, Smith I, White PF. Use of desflurane for outpatient anesthesia. *Anesthesiology* 1991; **75**: 197–203.
46. Watcha MF, Simeon RM, White PF, Stevens JL. Effect of propofol on the incidence of postoperative vomiting after strabismus surgery in pediatric outpatients. *Anesthesiology* 1991; **75**: 204–209.
47. Wrigley SR, Fairfield JE, Jones RM, Black AE. Induction and recovery characteristics of desflurane in day case patients: A comparison with propofol. *Anaesthesia* 1991; **46**: 615–622.
48. Hartung J. Nitrous oxide—it's enough to make you vomit (letter). *Anesthesiology* 1993; **78**: 403–405.
49. Watcha MF, White PF. In reply to Hartung J. 1993. *Anesthesiology* 1993; **78**: 405–406.
50. Tramèr M, Moore A, McQuay H. Prevention of vomiting after paediatric strabismus surgery: a systematic review using the numbers-needed-to-treat method. *British Journal of Anaesthesia* 1995; **75**: 556–561.
51. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical Epidemiology: A Basic Science for Clinical Medicine*, 2nd Edn. Boston/Toronto/London: Little, Brown and Company, 1991.
52. Oxman AD, Guyatt AH. A consumer's guide to subgroup analyses. *Annals of Internal Medicine* 1992; **116**: 78–84.
53. Moseley H, Kumar AY, Bhavani Shankar K, Rao PS, Homi J. Should air–oxygen replace nitrous oxide–oxygen in general anaesthesia? *Anaesthesia* 1985; **42**: 609–612.
54. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. *Journal of the American Medical Association* 1983; **249**: 1743–1745.
55. Bergström H, Bernstein K. Psychic reactions after analgesia without nitrous oxide for caesarean section. *Lancet* 1968; **ii**: 541–542.
56. Blacher RS. On awakening paralyzed during surgery. A syndrome of traumatic neurosis. *Journal of the American Medical Association* 1975; **234**: 67–68.
57. Cormack RS. Conscious levels during anaesthesia. *British Journal of Anaesthesia* 1993; **71**: 469–471.

British Journal of Anaesthesia 1996; **76**: 194–197

Cognitive failures after general anaesthesia for day-case surgery†

Y. TZABAR, A. J. ASBURY AND K. MILLAR

Summary

Patients are normally thought to have recovered from general anaesthesia within a few hours after day-case surgery. Previous recovery studies using objective psychometric tests showed a return to baseline values within this period. Nevertheless, patients are advised about what activities they should not undertake in the subsequent 24 h because it is feared that the residual anaesthetic effects may impair their ability. These studies did not follow patients out of hospital and their relevance to the real world is not known. Using the cognitive failures questionnaire, a standard measure of performance of everyday tasks, 54 patients were asked to report their own performance after general anaesthesia for the 3 days after discharge from hospital: 30 local anaesthetic patients were studied for comparison. The general anaesthesia group reported a highly significant greater incidence of cognitive failures after anaesthesia compared with the local anaesthesia group. This suggests that the residual effects of anaesthesia persist beyond 24 h. (*Br. J. Anaesth.* 1996; **76**: 194–197)

Key words

Anaesthesia, day-case. Psychological responses, postoperative.

When discharged after day-case surgery, patients are usually advised to avoid activities such as driving or operating hazardous machinery for 24 h after anaesthesia because residual effects may impair their cognitive ability and make them more liable to accidents. To estimate such residual effects, psychomotor and cognitive test batteries are often conducted within a few hours of the anaesthetic and show that cognitive performance has returned to preoperative baseline levels within 3–4 h.

It is possible, however, that such studies may underestimate residual impairment in patients because even when suffering severe fatigue or after-effects of sedation, individuals can muster sufficient resources to perform satisfactorily for short periods [1, 2]. There is at least anecdotal support for the idea that patients are impaired for several days after general anaesthesia; patients report forgetfulness or inability to concentrate. It is obviously important to know how recovering patients "perform" not only in hospital but also at home and it is possible that useful insight may be gained from patients' subjective assessment of their state, recorded several days after the event. We used the well-established cognitive failures questionnaire (CFQ) [3] which permits self-assessment of cognitive and psychomotor impairment, to assess day-case patients 3 days after anaesthesia. The CFQ has not been used, to our knowledge, in previous anaesthetic recovery research. However, while there are no existing data that might indicate its specific validity in such circumstances, its use in other patient groups confirms that it provides a reliable and valid measure of impaired cognitive function [4].

The objective of this study was to investigate cognitive function over 3 days after day-case anaesthesia using the CFQ.

Patients and methods

The study was approved by the Ethics Committee of the Victoria Infirmary, Glasgow.

The CFQ is a standardized instrument to collect information on cognitive lapses which occur in everyday life. It has been used to study cognitive failures in groups of healthy individuals and also in patients with physical and psychological problems such as chronic pain, terminal cancer and chronic fatigue syndrome [4]. The lapses usually indicate failure of perception, memory or a misdirected action. Such lapses are often minor but may have serious implications when driving or operating hazardous equipment at work or in the home.

The CFQ consists of 25 questions about lapses or mistakes that commonly occur in everyday life (see appendix). For each question, the respondent rates how frequently the error has occurred over the relevant time period. Each question can score from 0 to 4 so that the maximum score is 100. The higher the CFQ score, the greater the incidence of cognitive failures. The CFQ has the advantage of being easy to administer and provides a retrospective measure of integrated cognitive function over a period of time.

After obtaining informed consent, day-case patients undergoing surgery with general or local anaesthesia were asked to complete the CFQ with respect to the 3 days before admission. Patients receiving sedation (e.g. endoscopies), those aged less

---

Y. TZABAR*, MB, CHB, FRCA, Department of Anaesthetics, Victoria Infirmary, Langside Road, Glasgow G42 9TT. A. JOHN ASBURY, MB, CHB, FRCA, PHD, MD, University Department of Anaesthesia, Western Infirmary, Dumbarton Road, Glasgow G11 6NT. K. MILLAR, PHD, CPSYCHOL, FBPSS, Behavioural Sciences Group, University of Glasgow, 4 Lilybank Gardens, Glasgow G12 8QQ.

Accepted for publication: September 21, 1995.

*Present address for correspondence: Department of Anaesthetics, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XW.

†Presented in part at the Anaesthetic Research Society, Leeds Meeting, March 31–April 1, 1995 (*British Journal of Anaesthesia* 1995; 75: 231P).

than 18 yr, women undergoing termination of pregnancy and patients who were subsequently admitted after operation to the ward were excluded from the study. Patients took home a second CFQ with instructions to complete it 3 days after anaesthesia and return it in a pre-paid envelope. The second CFQ asked about the 3 days after discharge from hospital. Three days was chosen after a pilot study which found no difference between general and local anaesthesia groups at 7 days. This aspect of the methodology is considered further in the discussion.

The general anaesthetic technique was not standardized because the objective of this study was to detect alterations in cognitive function which could be found after general anaesthesia rather than to compare the effects of different agents and techniques. In the majority of cases, however, anaesthesia was induced with propofol, and maintained with a volatile agent, nitrous oxide, and a small dose of opioid. Limited opioids were used in the postoperative period according to local practice, and were not taken home by patients. No patient undergoing a procedure under local anaesthesia was sedated.

For obvious reasons it was impossible to allocate patients randomly to general or local anaesthesia groups. A wide variety of surgical procedures were carried out, including gynaecology, orthopaedic, dental, ENT and general surgery.

Data were analysed using the chi-square test for categorical data. The scores were treated as ordinal data and the Mann–Whitney and Wilcoxon rank tests were used for between-group and within-group hypothesis testing. $P < 0.05$ was considered significant.

Results

Eighty-two general anaesthesia and 39 local anaesthesia patients agreed to take part in the study. Of these, 54 (68 %) and 30 (77 %) returned their second questionnaire and the analysis is based on these samples. Patient data are shown in table 1. The general anaesthesia patients were significantly younger ($P < 0.01$, Mann–Whitney), and significantly more were female ($P < 0.05$, chi-square). This is an inevitable reflection of the work of the day surgery unit which includes a large gynaecology practice.

Pre- and post-anaesthetic CFQ scores for the two groups are shown in table 2. The general anaesthesia group reported significantly more cognitive failures during the 3 days after anaesthesia than during the same period before anaesthesia ($P < 0.01$, Wilcoxon). The local anaesthesia group showed no significant change. Moreover, a between-group analysis confirmed that while the general and local anaesthesia groups did not differ in pre-operative CFQ scores ($P > 0.05$, Mann–Whitney), the post-operative CFQ score in the general anaesthesia group was significantly higher than that in the local anaesthesia group ($P < 0.01$, Mann–Whitney).

Table 1 Patient data for the general (GA) and local anaesthesia (LA) groups

	GA group ($n = 54$)	LA group ($n = 30$)	P
Age (yr)			
Mean	34.4	48.7	< 0.01 (Mann–Whitney)
Median	33.0	49.0	
Range	19–60	22–77	
Sex (M/F)	13/41	14/16	< 0.05 (chi-square)

Table 2 CFQ scores before and after anaesthesia for the general (GA) and local anaesthesia (LA) groups

Group	Pre-anaesthetic score	Post-anaesthetic score	P (within groups)
GA group			
Mean	35.2	38.6	< 0.01
SD	13.1	16.0	
Range	7–73	2–77	
Median	35.5	39.0	
Interquartile range	25.5–42.8	27.5–46.8	
LA group			
Mean	33.0	31.2	ns
SD	11.6	14.0	
Range	5–54	7–54	
Median	34.0	34.5	
Interquartile range	25.5–40	21.5–39.8	
P (between groups)	ns	< 0.01	

Discussion

The CFQ data indicated that in a 3-day period after discharge, patients who underwent general anaesthesia experienced a significant increase in cognitive failures relative both to preoperative baseline values and to patients who underwent local anaesthesia. An initial conclusion would be that the after-effects of the anaesthetic, or the surgical procedure, continue to exert an adverse effect on cognition after general anaesthesia.

This conclusion would seem consistent with evidence from the few studies which have extended the assessment of cognitive recovery (in hospital) beyond the usual period of a few hours after return of consciousness. For example, *choice reaction time* has been shown to be impaired for 36 h [5] and *digit–symbol substitution* for 2–3 days [6] after general anaesthesia. Unfortunately, those studies which made direct comparisons between general and local anaesthesia recovery profiles are not helpful in the present case because they conducted assessments only in the immediate recovery stage and then at 3 months where, perhaps not surprisingly, no effects were found [7, 8].

There may have been some imprecision in the present assessment of the duration of impairment. Although the pilot study suggested that no impairment was present at 7 days, the sample sizes were rather small ($n = 10$) and therefore of low power. The choice of a 3-day assessment period was therefore somewhat arbitrary. A more extensive study may be required to determine the precise profile and duration of impairment, as judged by the CFQ.

The mechanism of residual impairment has been proposed as the residual effect of anaesthetic drugs on higher brain centres [9] or increased metabolic demands induced by the endocrine response to surgery [10]. While there is some evidence that general anaesthesia is indeed associated with a greater endocrine "stress" response than local anaesthesia, there is no associated evidence of differential cognitive impairment [8].

The fact that the general anaesthesia group reported greater impairment may be difficult to interpret because of the confounding factor of the different surgical procedures experienced compared with the local anaesthesia group. Not surprisingly, the general anaesthesia patients underwent more invasive surgery than the local anaesthesia group, for example laparoscopy compared with carpal tunnel decompression. Moreover, while the effect was statistically significant, it is difficult to judge its clinical significance because there are no appropriate normative data for the CFQ. The between-group difference was therefore suggestive but needs to be interpreted with caution. None the less, it is interesting that the general anaesthesia group did report greater impairment despite their significantly younger age composition.

There are further subjective biases that may affect patient responses even on standardized instruments [11–13]. The CFQ is a retrospective measure and is therefore subject to the vagaries of human memory. This may include not only forgetting incidents of cognitive failure, but also confabulation and misattribution of real incidents to the incorrect time period. For instance, some patients may have memories of profound impairment occurring in the immediate 24-h recovery period which they mistakenly believe and report to have occurred later during the 3-day study period. Such "false memories" can be difficult to assess. Moreover, patients completed the second questionnaire when unsupervised at home and it is possible that their responses were biased by the comments of partners and family on their condition. It is also possible, given the results of studies with other sedative agents, that patients in the general anaesthesia group may have "expected" to suffer impairment and that this expectation biased their responses in a negative way [12].

The fact that the CFQ itself enquires about impairment may bias some patients to respond positively. Given the standardized nature of the CFQ, one could not readily modify it in an attempt to "disguise" its true intent. However, future studies might contrast CFQ responses with performance on objective tests of recovery (reaction time, attention, etc.) whereby unimpaired performance on objective tests allied to subjective impairment on the CFQ might imply some bias in the latter assessment.

The response rates of 68 % and 77 %, respectively, for the general and local anaesthesia groups may detract slightly from the reliability of the conclusions. They may also introduce bias because those patients who had experienced particular impairment may have felt more motivated to return the questionnaire. A future study might consider interviewing all patients in the sample at home so as to ensure the recording of as full range of responses as possible. Another methodological improvement might be the inclusion of a non-operated, matched control group to take account of the fact that the incidence of cognitive failures probably varies from day to day even in the "normal" state.

As a tentative conclusion, the present results indicated that general anaesthesia patients perceived a residual impairment of their cognitive faculties over the 3 days after general anaesthesia. It would be important to extend the present study to include some degree of randomization between general and local anaesthesia in order to ensure equivalence in the procedures undergone. This presents some difficulty as such a study would be limited to operations that could be carried out equally well under both general and local anaesthesia and require that both patient and surgeon would agree to randomization rather than have a free choice. It would also be valuable to examine the degree of correlation between CFQ scores and the more commonly used psychomotor and cognitive test batteries. Recovery research has shown that psychological assessments have much to offer anaesthetic practice and there is considerable virtue in attempting to increase the "ecological validity" [1] of those assessments by demonstrating that their performance profiles are accurate reflections of the patient's state when discharged into the real world.

References

1. Herbert M. The duration of post anaesthetic mental impairment. In: Hindmarsh I, Jones JG, Moss E, eds. *Aspects of Recovery from Anaesthesia*. Chichester: Wiley, 1987; 103–112.
2. Millar K. The effects of anaesthetic and analgesic drugs. In: Smith AP, Jones DM, eds. *Handbook of Human Performance, vol. 2*. London: Academic Press, 1992; 337–385.
3. Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The cognitive failures questionnaire (CFQ) and its correlates. *British Journal of Clinical Psychology* 1982; **21**: 1–16.
4. Smith AP, Behan PO, Bell W, Millar K, Bakheit M. Behavioural problems associated with the chronic fatigue syndrome. *British Journal of Psychology* 1993; **84**: 411–423.
5. Herbert M, Healy TEJ, Bourke JB, Fletcher IR, Rose JM. Profile of recovery after general anaesthesia. *British Medical Journal* 1983; **286**: 1539–1542.
6. Chung F, Seyone C, Dyk B, Chung A, Ong D, Taylor A, Stone R. Age related cognitive recovery after general anesthesia. *Anesthesia and Analgesia* 1990; **71**: 217–224.
7. Nielson WR, Gelb AW, Casey JE, Penny FJ, Merchant RN, Manninen PH. Long term cognitive and social sequelae of general versus regional anesthesia during arthroplasty in the elderly. *Anesthesiology* 1990; **73**: 1103–1109.
8. Riis J, Lomholt B, Haxholdt O, Kehlet H, Valentin N, Danielsen U, Dyrberg V. Immediate and long term mental recovery from general versus epidural anaesthesia in elderly patients. *Acta Anaesthesiologica Scandinavica* 1983; **27**: 44–49.
9. Davison LA, Steinhelber JC, Eger EI, Stevens WC. Psychological effects of halothane and enflurane anesthesia. *Anesthesiology* 1975; **43**: 313–324.
10. Kehlet H. Stress-free surgery and anaesthesia. *Acta Anaesthesiologica Scandinavica* 1979; **23**: 503–504.
11. Poulton EC. *Bias in Quantifying Judgements*. London: Lawrence Erlbaum, 1989.
12. Finnigan F, Hammersley RH, Millar K. Effects of expectancy and alcohol on psychomotor performance. *Addiction* 1995; **90**: 661–672.
13. Millar K, Jelicic M, Bonke B, Asbury AJ. Assessment of preoperative anxiety: comparison of measures in patients awaiting surgery for breast cancer. *British Journal of Anaesthesia* 1995; **74**: 180–183.

Appendix

THE COGNITIVE FAILURES QUESTIONNAIRE

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. For each question the subject is asked to indicate how often these things have happened in the relevant time period by circling the appropriate number. (From: Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The cognitive failures questionnaire (CFQ) and its correlates. *British Journal of Clinical Psychology* 1982; 21: 1–16)

	Very often	Quite often	Occasionally	Very rarely	Never
1. Do you read something and find you haven't been thinking about it and must read it again?	4	3	2	1	0
2. Do you find you forget why you went from one part of the house to the other?	4	3	2	1	0
3. Do you fail to notice signposts in the road?	4	3	2	1	0
4. Do you find you confuse right and left when giving directions?	4	3	2	1	0
5. Do you bump into people?	4	3	2	1	0
6. Do you find you forget whether you've turned off a light or locked the door?	4	3	2	1	0
7. Do you fail to listen to people's names when you are meeting them?	4	3	2	1	0
8. Do you say something and realize afterwards that it might be taken as insulting?	4	3	2	1	0
9. Do you fail to hear people speaking to you when you are doing something else?	4	3	2	1	0
10. Do you lose your temper and regret it?	4	3	2	1	0
11. Do you leave important letters unanswered for days?	4	3	2	1	0
12. Do you find you forget which way to turn on a road you know well but rarely use?	4	3	2	1	0
13. Do you fail to see what you want in a supermarket (although it's there)?	4	3	2	1	0
14. Do you find yourself suddenly wondering whether you've used a word correctly?	4	3	2	1	0
15. Do you have trouble making up your mind?	4	3	2	1	0
16. Do you find you forget appointments?	4	3	2	1	0
17. Do you forget where you put something like a newspaper or a book?	4	3	2	1	0
18. Do you find you accidentally throw away the thing you want and keep what you meant to throw away—as in the example of throwing away the matchbox and putting the used match in your pocket?	4	3	2	1	0
19. Do you daydream when you ought to be listening to something?	4	3	2	1	0
20. Do you find you forget people's names?	4	3	2	1	0
21. Do you start doing one thing at home and get distracted into doing something else (unintentionally)?	4	3	2	1	0
22. Do you find you can't quite remember something although it's "on the tip of your tongue"?	4	3	2	1	0
23. Do you find you forget what you came to the shops to buy?	4	3	2	1	0
24. Do you drop things?	4	3	2	1	0
25. Do you find you can't think of anything to say?	4	3	2	1	0

British Journal of Anaesthesia 1996; **76**: 198–202

Use of i.v. insulin in well-controlled non-insulin-dependent diabetics undergoing major surgery

M. RAUCOULES-AIMÉ, Y. LABIB, J. LEVRAUT, P. GASTAUD, C. DOLISI AND D. GRIMAUD

Summary

We conducted a randomized, prospective study to assess the effect of i.v. insulin on blood glucose control, development of ketone bodies and hormonal changes in 60 well-controlled, non-insulin-dependent diabetics (NIDDM) undergoing major surgery. In group A, patients were given only 0.9% saline; in group B, patients were given insulin as a continuous i.v. infusion (1.25 u. h^{-1}); in group C, patients were given insulin 10 u. i.v. boluses every 2 h. Patients in all three groups were given insulin 5 u. when their intraoperative blood glucose concentration increased to greater than 11.1 mmol $litre^{-1}$. Blood glucose concentrations were measured every 15 min, from just before induction of anaesthesia to 2 h after surgery. Plasma lactate, pyruvate, ketone body, C-peptide and counter-regulatory hormone concentrations were also measured. Blood glucose concentrations in the three groups did not differ significantly. There was a mild-to-moderate increase in plasma ketone body concentrations in group A, but without any deleterious consequences. Plasma C-peptide concentrations decreased significantly in groups B and C, especially in patients given bolus injections of insulin. Plasma growth hormone concentrations also increased significantly in group B and C patients. This study indicated that the "no insulin–no glucose" regimen was a simple, effective way to control blood glucose in well-controlled NIDDM patients, provided blood glucose was measured frequently and insulin used appropriately. (*Br. J. Anaesth.* 1996; **76**: 198–202)

Key words

Complications, diabetes. Metabolism, insulin. Metabolism, glucose. Diabetes.

There is some controversy on the metabolic management of patients with non-insulin-dependent diabetes mellitus (NIDDM) undergoing surgery [1–4]. Clearly, poorly controlled NIDDM patients should be given insulin, while well-controlled ones undergoing minor surgery do not require any special treatment [1, 5, 6]. The case for the metabolic management of NIDDM patients undergoing major surgery with insulin is not simple [1, 4]. Insulin may induce hypoglycaemia and metabolic abnormalities [2], complicating the management of anaesthesia. Controlling blood glucose with insulin appears to provide little or no benefit over no-insulin treatment [7]. Some authors therefore propose giving insulin only when blood glucose concentrations exceed 11.1 mmol $litre^{-1}$, assuming there is adequate preoperative control and perioperative blood glucose monitoring [8], while others routinely give NIDDM patients insulin [1]. They point out that, in spite of hyperinsulinaemia, frequently found in these patients, hyperglycaemia, osmotic diuresis, ketosis and acidaemia may occur under stressful conditions.

We therefore conducted a randomized, prospective study to evaluate the effects of i.v. insulin on blood glucose control, ketone body development and hormonal changes in well-controlled NIDDM patients undergoing major surgery.

Patients and methods

We studied 60 NIDDM patients undergoing elective orthopaedic surgery (hip replacement, spinal surgery) or abdominal surgery (cholecystectomy, gastrectomy, bowel resection). The study was approved by the Ethics Committee of the University Hospital Centre and informed consent was obtained from all patients. Inclusion criteria were: fasting plasma blood glucose < 7.9 mmol $litre^{-1}$ and glycosylated haemoglobin (HbA_{1C}) less than 8% [8, 9]. Patients with impaired renal function (creatinine > 120 µmol $litre^{-1}$) or impaired hepatic function (based on routine liver function tests) were excluded from the study. None of the patients had been given insulin previously. Sulphonylurea hypoglycaemic drugs were discontinued the night before surgery, and biguanides 72 h before. All had fasted for 12–14 h before surgery.

Patients were allocated randomly to one of three groups. Group A ($n = 20$) patients were given only 0.9% saline 125 ml h^{-1} ("no insulin–no glucose"). Patients in groups B and C were given a continuous infusion of 5% glucose 6.25 g h^{-1} with i.v. short-acting insulin (Actrapid HM, Novo, France), started just before induction of anaesthesia. In group B ($n = 20$), patients were given insulin as a continuous infusion (1.25 u. h^{-1}) by an electrically driven syringe (40 u./31 ml 0.9% saline (1.25 u. = 1 ml)) [10]; patients in group C ($n = 20$) were given insulin 10 u. by direct i.v. bolus injection every 2 h [11]. Patients in all three groups were anaesthetized only

---

M. RAUCOULES-AIMÉ, MD, PHD, Y. LABIB, MD, J. LEVRAUT, MD, D. GRIMAUD, MD (Department of Anaesthesia); P. GASTAUD, MD (Department of Ophthalmology); C. DOLISI, MD (Department of Physiology); Hôpital Saint-Roch, 5 rue P. Dévoluy, Centre Hospitalier et Universitaire, 06006 Nice Cedex 1, France.
Accepted for publication: September 29, 1995.
Correspondence to M.R.-A.

when blood glucose concentration was 5.5–11.1 mmol litre^{-1}; if the concentration was < 5.5 mmol litre^{-1}, glucose was given; if it was > 11.1 mmol litre^{-1}, additional insulin (5 u.) was given as an i.v. bolus until blood glucose was < 11.1 mmol litre^{-1}. During surgery, all patients were given a bolus injection of insulin 5 u. whenever blood glucose exceeded 11.1 mmol litre^{-1}, with at least 60 min between doses. A second venous cannula was used to infuse other medications or 0.9 % saline for volume expansion (fluids containing glucose and lactate were prohibited).

All patients were premedicated with flunitrazepam 1–2 mg orally. All procedures were performed under general anaesthesia. Anaesthesia was induced with thiopentone 5 mg kg^{-1}, and tracheal intubation was facilitated with vecuronium 0.1 mg kg^{-1}. Fentanyl 2 µg kg^{-1} was used at induction and during anaesthesia in response to hypertension, tachycardia, or both. Anaesthesia was maintained with 0.8–1 % enflurane and 50 % nitrous oxide in oxygen. Neuromuscular block was maintained with vecuronium, which was not antagonized after surgery. Ventilation of the lungs was controlled to maintain end-tidal $P\text{CO}_2$ at 4.8–5.3 kPa.

The study began just before induction and ended 2 h after surgery. Capillary concentrations of glucose were measured every 15 min. Plasma ketone bodies (acetoacetate, β-hydroxybutyrate), lactate, pyruvate, C-peptide and counter-regulatory hormones (catecholamines, cortisol, glucagon, growth hormone) were measured in venous samples (S) taken just before induction (S1), during surgery (S2: 30 min after the beginning of cholecystectomy; 60 min for gastrectomy, bowel resection, hip replacement and spinal surgery), and immediately after completion of surgery and tracheal extubation (S3). Details of the assays have been published previously [10]. The following variables were recorded: capillary glucose concentrations; treatment failure (defined as blood glucose concentration < 3.3 mmol litre^{-1} or > 16.5 mmol litre^{-1}); total amount of insulin and number of additional boluses given; plasma acetoacetate and β-hydroxybutyrate : acetoacetate ratios at S1, S2, S3; plasma lactate, pyruvate concentrations and lactate : pyruvate ratios at S1, S2, S3; plasma C-peptide and counter-regulatory hormone concentrations at S1, S2, S3.

Data were analysed by two-way analysis of variance (ANOVA) for repeated measurements. Student's unpaired two-tailed *t* test was used to compare groups. Comparison of two time points within a group were made using Student's two-tailed *t* test for paired data. The resulting *P* values were adjusted by Bonferroni's method. ANOVA was used to compare the amount of insulin given in both groups and the quantities of fentanyl. β-hydroxybutyrate : acetoacetate and lactate : pyruvate ratios were compared using non-parametric tests. Non-parametric tests were also used to compare plasma growth hormone concentrations. The chi-square test was used for non-continuous variables. Results are expressed as mean (SEM). $P < 0.05$ was considered statistically significant. Statistical analyses were performed using a MacIntosh II computer with the Statview program.

Results

There were no significant differences between the groups in patient data, type or duration of surgery, duration of diabetes or preoperative control of glycaemia, determined by HbA_{1c}, fasting plasma glucose and capillary glucose concentrations measured just before induction of anaesthesia (table 1). The doses of fentanyl given to the three groups were similar (A: 665 (25) µg; B: 602 (25) µg; C: 650 (22) µg). Seven patients had blood glucose concentrations controlled by diet alone (two in group A, three in group B, two in group C). Six patients in group A, six in group B and five in group C were given blood products during surgery (packed red blood cells or plasma).

The distribution of all blood glucose concentrations (expressed as percentiles) measured every

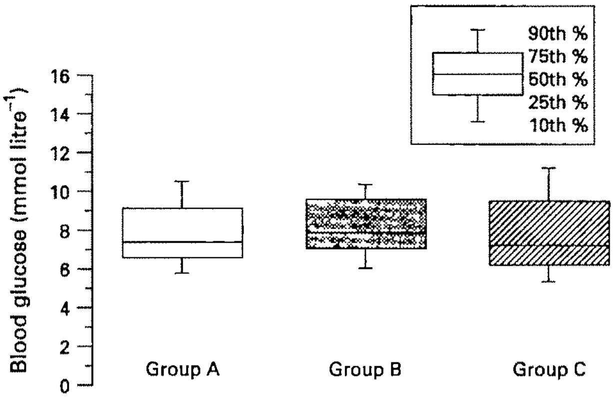


Figure 1 Distribution of blood glucose values measured every 15 min during the study, displayed as percentiles (%), for groups A (no insulin–no glucose), B (continuous infusion) and C (bolus).

Table 1 Patient data, blood glucose concentrations (BGC) just before induction of anaesthesia, haemoglobin A_{1c} (HbA_{1c}) and duration of diabetes in group A (no insulin–no glucose), group B (continuous infusion) and group C (bolus) (number or mean (range or SEM)). No significant differences between groups

	Group A ($n = 20$)	Group B ($n = 20$)	Group C ($n = 20$)
Sex distribution (M/F)	12/8	13/7	13/7
Age (yr)	61.9 (45–81)	64.5 (48–80)	61.1 (41–77)
Weight (kg)	70.2 (56–90)	69.1 (55–83)	76.1 (50–88)
BGC (mmol litre^{-1})	6.7 (4.4–9.6)	7.5 (4.9–13.5)	7.1 (5.5–12.3)
HbA_{1c} (%)	6.8 (5.3–8.0)	7.0 (6.1–7.9)	7.1 (5.7–8.0)
Duration of diabetes (yr)	7.0 (0.9)	8.1 (1.5)	8.0 (2.0)
Duration of surgery (h)	3.5 (0.3)	2.6 (0.4)	3.0 (0.3)

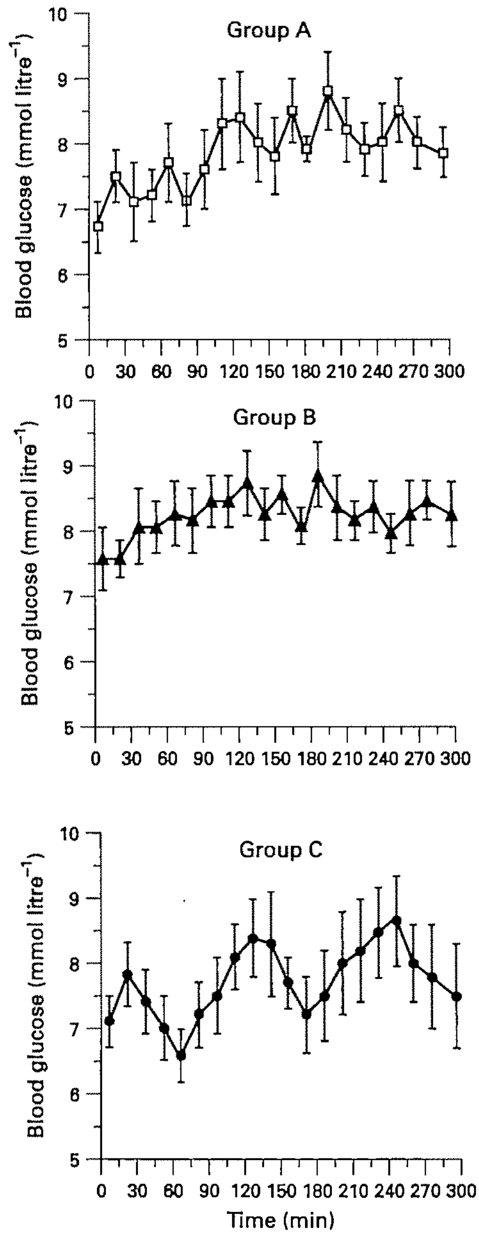


Figure 2 Mean (SEM) blood glucose concentrations measured every 15 min in groups A (no insulin–no glucose), B (continuous infusion) and C (bolus). No significant differences between groups.

15 min during the study in all groups is shown in figure 1. Blood glucose concentrations in the three groups were not significantly different (two-way repeated ANOVA) (fig. 2). Infusion of glucose was increased in three patients (one in group A, two in group B) just before induction of anaesthesia to offset low blood glucose concentrations (< 5.5 mmol litre^{-1}). The number of additional insulin boluses given when intraoperative blood glucose concentrations exceeded 11.1 mmol litre^{-1} was similar in all three groups (table 2). No case of hypoglycaemia (blood glucose < 3.3 mmol litre^{-1}) or hyperglycaemia (blood glucose > 16.5 mmol litre^{-1}) was encountered.

Plasma β-hydroxybutyrate concentration increased just before anaesthesia (S1) and gradually decreased during surgery ($P < 0.05$), except in group A, where concentrations remained increased (S2: 0.63 (0.10–1.19) mmol litre^{-1}; S3: 0.71 (0.12–1.08) mmol litre^{-1}) (table 3). Acetoacetate concentrations did not differ significantly (group A, S2: 0.39 (0.10–0.69) mmol litre^{-1}; S3: 0.45 (0.10–0.72) mmol litre^{-1}) and the β-hydroxybutyrate: acetoacetate ratio did not vary significantly with time. It remained > 1 in group A, but decreased in groups B and C ($P < 0.001$, $P < 0.01$). Plasma lactate and pyruvate concentrations increased significantly ($P < 0.05$ and $P < 0.01$) during surgery, with no differences between groups, although pyruvate concentration increased to a lesser extent in group A. The lactate:pyruvate ratio did not change throughout the study (table 3). There were no major metabolic problems during the postoperative period in any of the three groups.

Plasma C-peptide concentrations differed significantly between the groups ($P < 0.01$) (table 4). The time course of changes in the concentrations were also significantly different ($P < 0.0001$). C-peptide concentrations decreased significantly during surgery in groups B and C (table 4), especially in patients given bolus injections of insulin ($P < 0.001$), while plasma C-peptide concentrations remained stable in group A.

Plasma cortisol and catecholamine concentrations increased similarly during surgery in the three groups (table 4). Plasma glucagon concentrations remained stable. Plasma growth hormone concentrations were significantly different between groups ($P < 0.01$); they increased significantly in groups B and C ($P < 0.05$, $P < 0.01$) and remained constant in group A.

Discussion

The majority of diabetics undergoing surgery in Western countries are non-insulin-dependent. Nevertheless, there is no consensus on the best method of managing blood glucose concentrations of patients with well-controlled NIDDM undergoing major surgery, especially in the use of insulin [1, 5, 8]. The main metabolic complications in diabetics during surgery are hypoglycaemic reactions caused by exogenous insulin, hyperglycaemia, ketosis and acidaemia [8]. This study showed that the control of blood glucose was similar, whether or not patients

Table 2 Insulin given (mean (SEM or range)). $^{**}P < 0.01$, group A *vs* group B; $^{\dagger\dagger}P < 0.01$, group A *vs* group C; $^{\ddagger\ddagger}P < 0.01$, group B *vs* group C

	Group A ($n = 20$)	Group B ($n = 20$)	Group C ($n = 20$)
Total amount (u.)	3.4 (0–15)	11.5 (4–20)**	27.0 (20–37)††‡‡
Amount per hour (u. h^{-1})	0.6 (0–3.5)	2.4 (1.2–4.6)**	5.5 (4.0–8.3)††‡‡
Additional boluses (n)	0.50 (0–3)	1.3 (0–3)	0.6 (0–3)

Table 3 Mean (range) lactate, pyruvate, ketone body concentrations and lactate:pyruvate, β-hydroxybutyrate:acetoacetate concentration ratios before operation (S1), during surgery (S2) and after tracheal extubation (S3). Significant differences compared with preoperative values (S1): †$P < 0.05$; ††$P < 0.01$; †††$P < 0.001$; significant differences between groups: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

	S1	S2	S3
No insulin–no glucose			
Lactate (mmol litre^{-1})	1.4 (0.9–1.9)	1.9 (1.0–3.4)	2.1 (0.9–2.9)††
Pyruvate (μmol litre^{-1})	56 (36–81)	60 (33–107)	73 (40–123)†
Lactate:pyruvate ratio	25.2 (17.3–36.0)	26.6 (15.5–54.0)	26.2 (12.0–39.3)
β-Hydroxybutyrate (mmol litre^{-1})	0.43 (0.10–1.19)	0.63 (0.10–1.40)	0.71 (0.18–1.40)†
Acetoacetate (mmol litre^{-1})	0.37 (0.03–0.75)	0.39 (0.04–0.98)	0.45 (0.10–1.10)
β-Hydroxybutyrate:acetoacetate	1.23 (0.15–2.64)	1.60 (0.30–4.10)	1.68 (0.20–3.00)
Continuous infusion			
Lactate (mmol litre^{-1})	1.5 (0.6–2.7)	1.9 (0.9–3.3)	2.1 (0.9–3.9)†
Pyruvate (μmol litre^{-1})	55 (15–91)	65 (22–147)	79 (27–123)†
Lactate:pyruvate ratio	26.5 (14.5–43.3)	24.3 (15.5–35.4)	25.5 (17.7–36.6)
β-Hydroxybutyrate (mmol litre^{-1})	0.70 (0.08–2.21)	0.34 (0.07–1.87)	0.19 (0.09–0.89)†***
Acetoacetate (mmol litre^{-1})	0.55 (0.07–1.60)	0.45 (0.03–1.50)	0.39 (0.03–1.66)
β-Hydroxybutyrate:acetoacetate	1.31 (0.10–5.00)	0.75 (0.13–4.70)	0.50 (0.14–3.81)†***
Bolus			
Lactate (mmol litre^{-1})	1.6 (0.9–2.5)	2.0 (1.0–3.5)	2.3 (1.1–3.8)††
Pyruvate (μmol litre^{-1})	60 (20–94)	90 (40–199)*	102 (42–130)†††**
Lactate:pyruvate ratio	25.5 (15.3–36.2)	22.5 (13.3–37.7)	23.1 (12.5–31.1)
β-Hydroxybutyrate (mmol litre^{-1})	0.55 (0.09–2.25)	0.15 (0.07–0.56)†*	0.14 (0.07–0.39)†***
Acetoacetate (mmol litre^{-1})	0.31 (0.08–1.10)	0.27 (0.05–0.99)	0.18 (0.05–0.55)
β-Hydroxybutyrate:acetoacetate	1.56 (0.15–2.38)	0.58 (0.10–3.70)†**	0.79 (0.15–5.41)**

Table 4 Mean (range) hormonal data before operation (S1), during surgery (S2) and after tracheal extubation (S3). Significant differences compared with preoperative values (S1): †$P < 0.05$, ††$P < 0.01$, †††$P < 0.001$; significant differences between groups: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

	S1	S2	S3
No insulin–no glucose			
Noradrenaline (nmol litre^{-1})	2.17 (0.42–6.40)	4.09 (0.82–9.11)	6.41 (0.62–15.30)†
Adrenaline (nmol litre^{-1})	0.47 (0.19–1.30)	0.83 (0.20–2.28)	1.58 (0.37–7.94)
Cortisol (nmol litre^{-1})	345 (180–760)	468 (110–1000)	668 (270–1490)††
Growth hormone (μiu ml^{-1})	0.9 (0.4–6.6)	2.6 (0.5–9.5)	2.7 (0.5–12.7)
Glucagon (pmol litre^{-1})	134 (38–439)	126 (32–457)	150 (32–476)
C-peptide (nmol litre^{-1})	2.65 (1.35–3.83)	2.76 (1.35–5.61)	2.27 (0.80–3.42)
Continuous infusion			
Noradrenaline (nmol litre^{-1})	2.16 (0.50–5.03)	3.95 (0.49–7.37)	4.74 (0.48–7.35)††
Adrenaline (nmol litre^{-1})	0.95 (0.30–3.97)	2.27 (0.50–3.46)	3.63 (0.46–9.51)
Cortisol (nmol litre^{-1})	372 (140–660)	450 (200–1600)	757 (120–1900)††
Growth hormone (μiu ml^{-1})	1.4 (0.3–5.3)	6.6 (0.8–25.2)†*	5.7 (1.1–15.0)
Glucagon (pmol litre^{-1})	174 (68–555)	206 (52–518)	169 (55–523)
C-peptide (nmol litre^{-1})	2.18 (1.08–3.47)	1.82 (0.70–3.00)*	1.50 (0.30–3.22)†*
Bolus			
Noradrenaline (nmol litre^{-1})	1.67 (0.87–3.46)	2.76 (0.80–6.45)	4.34 (1.00–7.25)†
Adrenaline (nmol litre^{-1})	0.48 (0.28–1.10)	1.33 (0.49–3.57)	1.89 (0.50–5.32)
Cortisol (nmol litre^{-1})	442 (270–900)	859 (180–1600)†	1024 (280–1600)††
Growth hormone (μiu ml^{-1})	1.1 (0.3–2.2)	6.5 (1.6–16.0)††**	7.7 (1.1–16.5)††**
Glucagon (pmol litre^{-1})	104 (45–247)	96 (33–264)	106 (42–259)
C-peptide (nmol litre^{-1})	2.39 (0.91–3.93)	1.29 (0.86–1.90)†††***	1.02 (0.41–1.53)†††***

were given insulin. The "no insulin–no glucose" patients developed mild-to-moderate concentrations of ketone bodies.

Some authors believe that well-controlled NIDDM patients do not require special treatment before and during surgery [5, 6, 8], and that insulin therapy should be considered only when intraoperative blood glucose concentrations exceed 11.1 mmol litre^{-1}. This value was proposed because the renal threshold for glucose is 10.0–11.1 mmol litre^{-1} in most patients with normal renal function [12]. Osmotic diuresis results in water and electrolyte losses, hyperosmolarity and impaired CNS function if this level is exceeded. The literature also suggests that impaired wound healing and strength, and impaired phagocytic function may occur when plasma glucose concentrations exceed 11.1 mmol litre^{-1} [3, 13, 14]. Intraoperative blood glucose control was good in most patients on the "no insulin–no glucose" regimen in our study. These finding are consistent with those of Fletcher, Langman and Kellock for minor and moderate surgery [15]. Fasting was probably the cause of these stable blood glucose concentrations [16], because glucose given without insulin can result in marked hyperglycaemia [11, 17]. Fasting and a lower insulin:glucagon ratio were also responsible for the accelerated ketogenesis in the "no insulin–no glucose" group. But, because of residual endogenous insulin secretion in our patients, the development of ketone bodies was limited, and without any deleterious consequences. Ketogenesis was similar to that of normal subjects after short-term starvation [16]. Concentrations of lactate and pyruvate in the insulin-treated patients were increased, presumably as a result of insulin inhibiting gluconeogenesis and increased extrahepatic lactate production from glucose [16]. The lactate:pyruvate ratios were within normal limits for venous blood samples and were not affected by insulin administration. Thus, our results suggest that the "no insulin–no glucose" regimen provided sufficient metabolic control during the operative period and might even be preferable as it avoids the risk of hypoglycaemia. The incidence of hypoglycaemia was 5–10 % whatever insulin regimen was used [10]. While our study was relatively short, it is always possible that some metabolic disturbance may occur later, but no major metabolic problem was identified during the postoperative period.

The decrease in plasma C-peptide concentrations in groups B and C probably resulted from negative feedback by exogenous insulin on pancreatic insulin secretion. This decrease was even more significant in the group treated with large bolus doses of insulin. This inhibition develops over a few hours after insulin therapy is initiated in non-surgical situations [18]. The lack of increase in plasma GH in the "no insulin–no glucose" group appears to be surprising, because there is usually a gradual increase in GH during stress, which parallels that of cortisol and takes place a few minutes after induction of anaesthesia [19]. It has been shown that elevated plasma ketone body concentrations decrease the release of GH [20, 21]. The increase in GH concentrations in groups B and C may also result from stimulation of GH release by exogenous insulin [20]. However, this difference in growth hormone concentration did not alter blood glucose. The deleterious effect of increased growth hormone on blood glucose in diabetics is probably not as pronounced as the effect of catecholamines and cortisol [22]. This lack of difference in blood glucose concentration may also be caused by administration of exogenous insulin, which counteracts the effect of growth hormone on glucose metabolism.

Thus this study indicated that the "no insulin–no glucose" regimen was a simple, effective way of controlling blood glucose in well-controlled NIDDM patients, provided that blood glucose was measured frequently and insulin used as appropriate.

References

1. Alberti KGMM. Diabetes and surgery. *Anesthesiology* 1991; 74: 209–211.
2. Thompson J, Husband DJ, Thai AC, Alberti KGMM. Metabolic changes in the non-insulin-dependent diabetic undergoing minor surgery: Effect of glucose–insulin–potassium infusion. *British Journal of Surgery* 1986; 73: 301–304.
3. Milaskiewicz RM, Hall GM. Diabetes and anaesthesia: The past decade. *British Journal of Anaesthesia* 1992; 68: 198–206.
4. Hirsch IB, McGill JB. Role of insulin in management of surgical patients with diabetes mellitus. *Diabetes Care* 1990; 13: 980–991.
5. Podolsky S. Management of diabetes in the surgical patient. *Medical Clinics of North America* 1982; 66: 1361–1372.
6. Schade DS. Surgery and diabetes. *Medical Clinics of North America* 1988; 72: 1531–1543.
7. Thomas DJ, Platt HS, Alberti KGMM. Insulin infusion (GIK) in the treatment of type 2 (non-insulin-dependent) diabetes during the perioperative period. *British Journal of Surgery* 1986; 73: 898–901.
8. Hirsch IB, McGill JB, Cryer PE, White PF. Perioperative management of surgical patients with diabetes mellitus. *Anesthesiology* 1991; 74: 346–359.
9. Rosenstock J, Raskin P. Surgery. Practical guidelines for diabetes management. *Clinical Diabetes* 1987; 5: 49–61.
10. Raucoules-Aimé M, Ichai C, Roussel LJ, Romagnan MJ, Gastaud P, Dolisi C, Grimaud D. Comparison of two methods of i.v. insulin administration in the diabetic patient during the perioperative period. *British Journal of Anaesthesia* 1994; 72: 5–10.
11. Walts LF, Miller J, Davidson MB, Brown J. Perioperative management of diabetes mellitus. *Anesthesiology* 1981; 55: 104–109.
12. Elsas L, Rosenberg, L. Renal glycosuria. In: Earley L, Gottschalk C, eds. *Strauss and Welt's Diseases of the Kidney*, 3rd Edn. Boston: Little Brown, 1979; 1021–1028.
13. McMurray JF Jr. Wound healing with diabetes mellitus. *Surgical Clinics of North America* 1984; 61: 769–778.
14. Yue DK, McLennan S, Marsh M, Mai YW, Spaliviero J, Delbridge L, Reeve J, Turtle JR. Effects of experimental diabetes, uremia, and malnutrition on wound healing. *Diabetes* 1987; 36: 295–299.
15. Fletcher J, Langman MJS, Kellock TD. Effect of surgery on blood-sugar levels in diabetes mellitus. *Lancet* 1965; 2: 52–54.
16. Alberti KGMM, Thomas DJ. The management of diabetes during surgery. *British Journal of Anaesthesia* 1979; 51: 693–710.
17. Brenner WI, Lansky Z, Engleman RM, Stohl WM. Hyperosmolar coma in surgical patients: An iatrogenic disease of increasing incidence. *Annals of Surgery* 1973; 178: 651–655.
18. Liljenquist JE, Horwitz DL, Jennings AS, Chiasson JL, Keller U, Rubenstein AH. Inhibition of insulin secretion by exogenous insulin in normal man as demonstrated by C-peptide assay. *Diabetes* 1978; 27: 563–570.
19. Weissman C. The metabolic response to stress: An overview and update. *Anesthesiology* 1990; 73: 308–327.
20. Johnston DG, Davies RR, Prescott PW. Regulation of growth hormone secretion in man: A review. *Journal of the Royal Society of Medicine* 1985; 78: 319–327.
21. Quabbe HJ. Hypothalamic control of GH secretion: Pathophysiology and clinical implications. *Acta Neurochirurgica* 1985; 75: 60–71.
22. Raucoules-Aimé M, Lugrin D, Boussofara M, Gastaud P, Dolisi C, Grimaud D. Intraoperative glycaemic control in non-insulin-dependent and insulin-dependent diabetes. *British Journal of Anaesthesia* 1994; 73: 443–449.

British Journal of Anaesthesia 1996; **76**: 203–208

Pulmonary uptake of sufentanil during and after constant rate infusion

F. BOER, E. OLOFSEN, J. G. BOVILL, A. G. L. BURM, A. HAK, M. GEERTS AND K. E. WETSELAAR

Summary

We have studied the pulmonary uptake of sufentanil in patients during and after a short infusion of the drug. We studied 10 patients undergoing elective coronary artery bypass surgery during anaesthesia with 0.4–0.8% enflurane, before surgery. Sufentanil 50 μg min^{-1} was given over 10 min by a constant rate infusion. During infusion and for 20 min thereafter, blood samples were obtained from the distal port of the pulmonary artery catheter and from a radial artery catheter. Uptake and release of sufentanil into and from the lungs were examined by mass balance and compartmental analyses. At the end of the infusion a mean of 48.9 (SD 18.6)% of the dose was retained in the lungs, and 20 min after infusion retention was 18.4 (22.4)%. Smokers had significantly higher pulmonary retention of sufentanil. The pulmonary volume of distribution of sufentanil, estimated from the two-compartment model, was 20.9 (7.7) litre. We conclude that pulmonary uptake of sufentanil is significant, if the drug is given as an infusion. (*Br. J. Anaesth.* 1996; **76**: 203–208)

Key words

Analgesics opioid, sufentanil. Lung, metabolic function. Pharmacokinetics, sulfentanil. Analgesic techniques, infusion.

Sufentanil, a synthetic opioid, undergoes significant first-pass pulmonary uptake after i.v. bolus injection. In cardiothoracic patients, first-pass retention of sufentanil is approximately 60%, considerably higher than that of alfentanil (10%) and morphine (7%) [1]. Pulmonary uptake and release *in vivo* are studied usually with a double-indicator dilution technique, because this requires only arterial blood samples. However, the technique can measure extraction and retention in the lungs only before recirculation of the indicator occurs. Studies of pulmonary uptake and release beyond the first-pass period require both pulmonary arterial and arterial blood sampling. Uptake and release can then be examined using mass balance principles [2].

The mass balance of a drug over an organ is the time integral of organ blood flow times the arterio-venous concentration difference. If flow or concentration, or both, change rapidly, frequent measurement of blood flow and frequent blood sampling are required to obtain accurate results. Mass balance principles can be applied to the study of pulmonary uptake in patients, as pulmonary blood flow can be measured. However, the frequency of manual determination of cardiac output so far has limited the accuracy of mass balance analysis. Recently, a semi-continuous (thermodilution) cardiac output measurement technique has become available, which allows automated and frequent cardiac output measurement [3, 4]; in cardiac surgical patients, this has a mean relative error of 0.8%, an SD of the relative error of 8% and a regression coefficient of 0.87 compared with the bolus thermodilution technique [5, 6]. This technique, in combination with high frequency, automated blood sampling, should allow *in vivo* determination of pulmonary uptake using mass balance analysis.

The aim of our study was to investigate pulmonary uptake and release of sufentanil during and after a short (10 min) constant rate infusion of the drug, using a mass balance technique. Results of the mass balance analysis were compared with those obtained from a physiological compartmental analysis of pulmonary and radial arterial concentrations.

Patients and methods

The study was approved by the local medical Ethics Committee and all patients gave informed consent. We studied 10 patients undergoing elective aorto-coronary bypass surgery. Patients with unstable angina pectoris, poor left ventricular function (defined as an ejection fraction > 0.5, left ventricular end-diastolic pressure < 12 mm Hg or good regional left ventricular wall movement), valvular abnormalities or pulmonary disease were excluded.

Premedication comprised lorazepam 3–5 mg orally, 90 min before arrival in the operating theatre. Patients who were receiving β-adrenoceptor blocking drugs, calcium entry blocking drugs and nitrates continued on these medications until the morning of surgery. In the operating theatre ECG electrodes were attached and cannulae inserted into a peripheral

---

F. BOER, MD, PHD, E. OLOFSEN, MSC, J. G. BOVILL, MD, PHD, FFARCSI, A. G. L. BURM, PHD, A. HAK, BSC, M. GEERTS, BSC, K. E. WETSELAAR, Department of Anaesthesiology, University Hospital Leiden, Postbox 9600, 2300 RC Leiden, The Netherlands. Accepted for publication: October 6, 1995.

vein and a radial artery. After induction of anaesthesia, a pulmonary artery catheter was inserted via an internal jugular vein. Before and during induction of anaesthesia, Gelofusin 500 ml was infused to reduce the effect of administration of sufentanil on haemodynamic stability. The peripheral infusion cannula was then maintained patent by a slowly running infusion of 2.5 %–0.45 % glucose–saline until the experiment started. The total volume of glucose–saline administered to individual patients varied between 100 and 300 ml.

Anaesthesia was induced with etomidate 0.3 mg kg^{-1} and alfentanil 30 μg kg^{-1}. Pancuronium 100 μg kg^{-1} was given for neuromuscular block. Anaesthesia was maintained with enflurane with an inspired concentration of 0.6–1.2 %. After intubation of the trachea, the lungs of the patients were ventilated with an oxygen in air mixture ($F\text{I}_{O_2} = 0.5$) by intermittent positive pressure ventilation at a frequency of 12 b.p.m. Minute volume was adjusted to maintain an end-expiratory carbon dioxide concentration of 4.5–5 %. Arterial oxygen and carbon dioxide tensions were measured in arterial blood samples obtained at the start and the end of the 30-min study.

After induction of anaesthesia and placement of the pulmonary artery catheter, when the condition of the patient was stable, the experiment was started. The condition of the patient was considered stable when anaesthesia was adequate, systolic arterial pressure was 100 mm Hg or more, cardiac index was more than 2.1 litre min^{-1} m^{-2} and $F\text{E}'_{CO_2}$ was 4.5–5 %. Sufentanil (Sufenta Forte) 50 μg ml^{-1} was infused at a rate of 1 ml min^{-1} via a peripheral i.v. catheter for 10 min, using a syringe pump (Ohmeda 9000, Strector, UK). The volume infused during the 10-min infusion period was noted. Samples were obtained from the pulmonary artery via the distal port of the pulmonary artery catheter and from the radial artery via the radial artery catheter. Blood was sampled with the aid of a specially constructed, computer-controlled syringe pump and fraction collector. The sample size was equal to the deadspace in the catheter and extension lines to the sample pump and samples were withdrawn over 8 s. Samples were obtained at high frequency, 1 per 10 s, at the start and end of the infusion and at lower frequencies at other time. Sampling was continued until 20 min after the end of the infusion. Both the infusion and sampling were controlled by computer (Atari Portfolio, Okasaki, Japan), interfaced to the syringe pump and the sampling machine via a serial RS232 communication channel.

Cardiac output was measured continuously with the aid of a pulmonary artery catheter (Intellicath, Baxter-Edwards) connected to the cardiac output computer (Vigilance, Baxter Healthcare Corporation). The cardiac output computer gives the mean cardiac output over the previous 3–4 min, depending on the signal-to-noise ratio, and is updated every 45 s. Measurement of cardiac output, arterial pressure, electrocardiogram, function of the infusion pump and of the sampling pump were logged with a data acquisition system (model PS1600, 3T Twente Technology Transfer, Enschede, The Netherlands).

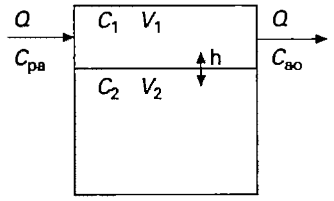


Figure 1 Two-compartment model used to described pulmonary retention of sufentanil. C_{pa} and C_{ao} = concentrations in the pulmonary artery and aorta, respectively, Q = blood flow through the lungs, V_1 and V_2 = volumes of the first and second compartments, C_1 and C_2 = concentrations in the first and second compartments, h = equilibration constant.

Whole blood samples were stored at −20 °C until assay for sufentanil with a highly specific radioimmunoassay [1]. The detection limit was 0.4 ng ml^{-1}, and the coefficients of variation of spiked concentrations of 40 and 100 ng ml^{-1} were 4.5 % and 4.2 %, respectively.

CALCULATIONS

Mass balance analysis

Calculation of mass balance analysis was performed as described by Upton and co-workers [2]. For each sampling time the next flux of sufentanil into or out of the lungs, $J_{net,t}$ was calculated as:

$$J_{net,t} = Q_t(C_{pa,t} - C_{ra,t})$$

where Q = cardiac output (ml s^{-1}), C_{pa} = pulmonary arterial sufentanil concentration and C_{ra} = arterial sufentanil concentration. Subsequently, the net mass balance ($M_{net,t}$) of sufentanil at each sampling time was calculated by integration of the flux $J_{net,t}$:

$$M_{net,t} = \int_0^t J_{net,u}\,du$$

where u = a dummy variable. The integral was approximated using the trapezoidal rule. The percentage of the administered dose of sufentanil which was retained in the lungs at the end of the infusion (t = 600 s) and at the end of the experiment (t = 1800) was calculated as:

$$\text{Retention}_t = \frac{M_{net,t}}{\text{dose}} 100\,\%$$

where the dose was calculated from the infused volume and the concentration of sufentanil in the infusion.

Compartmental analysis

A physiologically based, non-eliminating, membrane-limited, two-compartment model (see for example Gerlowski and Jain [7]), was fitted to the arterial sufentanil concentrations. This model (fig. 1) consists of two-compartments (with volumes V_1 and V_2) in which complete mixing of the drug is assumed to take place. The passive transfer from one compartment to the other is described by a mass transfer coefficient h. Drug transport to V_1 is cardiac output, Q, times the concentration in the pulmonary artery. Transport from the lungs to the effluent blood (left atrium, aorta and the side branches of the aorta) is cardiac output times the concentration in V_1. The change in concentration of the drug (C_1, C_2) in the two compartments is described by the following equations:

$$V_1\frac{\mathrm{d}C_1}{\mathrm{d}t} = Q_t(C_{\mathrm{pa},t} - C_{1,t}) - h(C_1, t - C_{2,t})$$

$$V_2\frac{\mathrm{d}c_2}{\mathrm{d}t} = h(C_{1,t} - C_{2,t})$$

$$C_{\mathrm{ra},t} = AC_{1,t}$$

where A = a proportionality constant, as this significantly improved the fits. This proportionality constant theoretically has a value of 1. However, when drug is lost in the pulmonary circulation (by excretion or elimination), the proportional constant becomes less than 1. The arterial (pulmonary venous) concentrations were predicted by solving the differential equations using Euler's method with linear interpolation of $C_{\mathrm{pa},t}$, $C_{\mathrm{ra},t}$ and Q_t such that the time steps were 1 s. An unweighted iterative non-linear regression technique was used to estimate the model variables V_1, V_2, h and A. If cardiac output is taken as constant, the variables can be transformed to those describing a classical compartmental model. These variables were calculated as $k_{12} = h/V_1$, $k_{21} = h/V_2$ and $k_{10} = Q/V_1$. Cardiac output used for this calculation was the mean cardiac output of the study period.

STATISTICS

Haemodynamic data and arterial blood-gas analyses were analysed by repeated measures analysis of variance, followed by Newman–Keul's multiple range tests when significant differences were observed in the analysis of variance. Unpaired t test analysis was used to compare retention of sufentanil between smokers and non-smokers. $P < 0.05$ was considered statistically significant.

Results

Patient data are presented in table 1. Most of the patients received β adrenoceptor blocking agents and four of the 10 patients were smokers. Haemodynamic data and blood-gas values of the samples obtained during the experiment are given in table 2. Administration of sufentanil significantly decreased heart rate and mean arterial pressure by the end of infusion. At the end of the experiment mean arterial pressure returned to values close to those at the start of the sufentanil infusion, while cardiac output was significantly lower by that time. Blood-gas values did not change significantly during the study.

Table 1 Patient data for those in whom sufentanil pulmonary uptake was studied during and after a 10-min infusion of the drug (mean (SD) or number)

Variable	
No. of patients	10
Height (cm)	173 (6)
Weight (kg)	80.3 (16.8)
Medications	
β blockers	7/10
Nitrates	2/10
Ca entry blockers	8/10
Smokers	4/10

Infusion of sufentanil resulted in a rapid increase in pulmonary arterial concentrations to a plateau and systemic arterial concentrations slowly increased but never reached pulmonary arterial concentrations (fig. 2). After stopping the infusion of sufentanil, pulmonary arterial concentrations decreased rapidly to values below those of systemic arterial concentrations. Both pulmonary arterial and systemic arterial concentrations decreased slowly during the 20 min after infusion.

Net flux of sufentanil to the lungs, J_{net}, was considerable in all patients during the infusion. Figure 3 shows the individual J_{net} time curves for all patients (upper panel) and the mean J_{net} time plot of the 10 patients (lower). There were considerable differences between patients during infusion of sufentanil, and these differences appeared to be smaller after stopping the infusion of sufentanil. During the infusion, J_{net} increased to a peak 3–4 min after starting the infusion and then decreased gradually. This gradual decrease in J_{net} indicates partitioning to the lungs when lung tissue concentrations increase. At the end of sufentanil infusion, net flux changed from a positive to a negative value, indicating release of sufentanil from the lungs.

Mass balance analysis of pulmonary arterial and radial arterial sufentanil concentrations showed significant uptake of sufentanil in the lungs. Figure 4 gives the individual mass balance curves (upper panel) and the mean mass balance curves of the 10 patients (lower panel). At the end of infusion, 48.9 (18.6) % of the administered dose of sufentanil was retained in the lungs. At the end of the experiment, 20 min after stopping the sufentanil infusion, 18.4 (22.8) % of the administered dose were retained in the lungs. Smokers had significantly higher pulmonary retention of sufentanil. At the end of infusion, pulmonary retention of sufentanil was 64.6 (11.9) % in smokers and 38.5 (14.4) % in non-smokers. This difference was statistically significant ($P = 0.0017$). At the end of the study, pulmonary retention had decreased to 34.9 (21.3) % in smokers and 7.4 (17.3) % in non-smokers. This difference was no longer significant ($P = 0.054$). Smokers and non-smokers were similar with regard to preoperative medication. There were no differences between those patients receiving β blocking agents and those who did not receive these drugs before operation (7 *vs* 3).

An example of the predicted arterial concentration–time curve from the physiologically based, two-compartmental model analysis is given in figure 5 together with the measured concentrations. The results of the compartmental analysis of pulmonary uptake are given in table 3 for each patient. The proportionality factor A was very close to 1, suggesting that sufentanil was not lost in the pulmonary circulation. There was no difference in any of the model variables between smokers and non-smokers.

Table 2 Haemodynamic data and arterial blood-gas values during and after a 10-min infusion of sufentanil at a rate of 50 µg min^{-1} (mean (SD)). * Significant difference from the start of the infusion ($P < 0.05$)

Variable	Start of infusion	End of infusion	End of experiment
Haemodynamics			
Heart rate (beat min^{-1})	70 (12)	65 (11)*	62 (11)*
Mean arterial pressure (mm Hg)	89 (12)	67 (14)*	76 (20)
Mean pulmonary arterial pressure (mm Hg)	24 (10)	24 (6)	25 (7)
Cardiac output (litre min^{-1})	6.21 (1.36)	6.13 (1.48)	5.32 (1.34)*
Arterial blood-gas values			
pH	7.39 (0.03)		7.39 (0.04)
Pa_{CO_2} (kPa)	5.6 (0.5)		5.6 (0.5)
Sa_{O_2} (%)	98 (2)		98 (2)

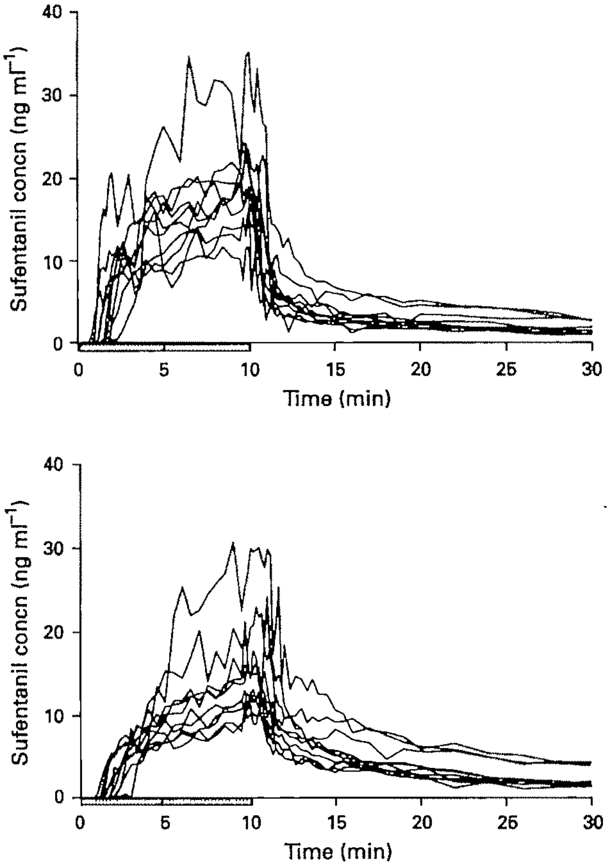


Figure 2 Pulmonary arterial (top) and systemic arterial (bottom) sufentanil concentration–time curves for the 10 patients during and after infusion of sufentanil 50 µg min^{-1} for 10 min (indicated by the bar).

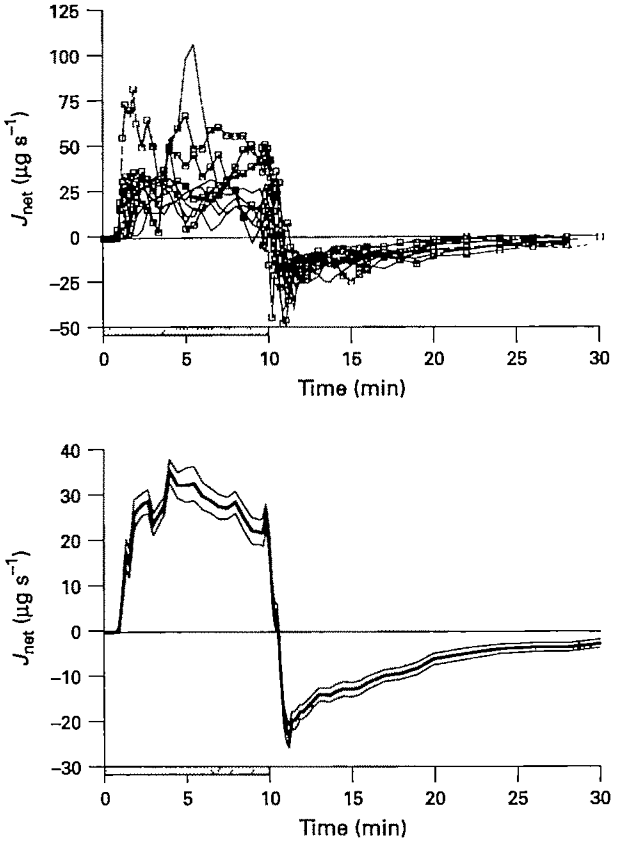


Figure 3 Individual pulmonary sufentanil flux (J_{net}) time curves (top), and mean (thick line) and 95 % confidence intervals of the mean (thin lines) of the pulmonary sufentanil J_{net} time curve (bottom) for the 10 patients during and after a 10-min infusion of sufentanil at a rate of 50 µg min^{-1} (indicated by the bar). □ = Curves of smokers.

Discussion

We have shown that at the end of a 10-min infusion of sufentanil, almost 50 % of the administered dose was retained in the lungs. After stopping the infusion, sufentanil disappeared slowly from the lungs, so that 20 min after infusion, 18.6 % of the administered dose was retained in the lungs. Smokers demonstrated higher pulmonary retention at the end of infusion. The mean estimated total volume of distribution of sufentanil was 20.9 litre.

Our findings are comparable with those of Taeger and co-workers [8]. They studied pulmonary retention after i.v. bolus injection of fentanyl and alfentanil mixed with indocyanine green. First-pass retention was examined with a double-indicator dilution technique. After the first-pass period, a mass balance technique was used and both arterial and pulmonary arterial samples were obtained. For calculation of the mass balance, they assumed that the amount of fentanyl remaining after first-pass, calculated as the product of first-pass retention and dose administered, can be taken as the initial amount in the lungs that can be used for the mass balance calculation. The first-pass retention of a bolus of fentanyl was 43–87 % and that of alfentanil 36–80 %. Disappearance of fentanyl from the lungs could be described by a biexponential function with half-lives of 0.22 and 5.78 min.

Alfentanil kinetics could not be studied adequately. As no pulmonary arterial samples were obtained

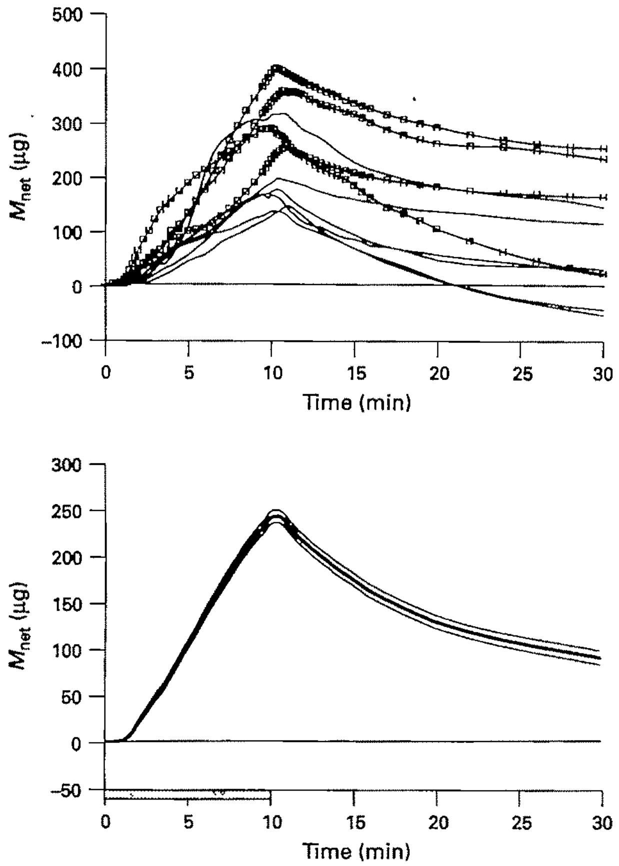


Figure 4 Individual pulmonary sufentanil mass balance (M_{net}) time curves (top), and mean (thick line) and 95 % confidence interval of the mean (thin lines) of the pulmonary sufentanil M_{net} time curve (bottom) for the 10 patients during and after a 10-min infusion of sufentanil at a rate of 50 μg min^{-1} (indicated by the bar). □ = Curves of smokers.

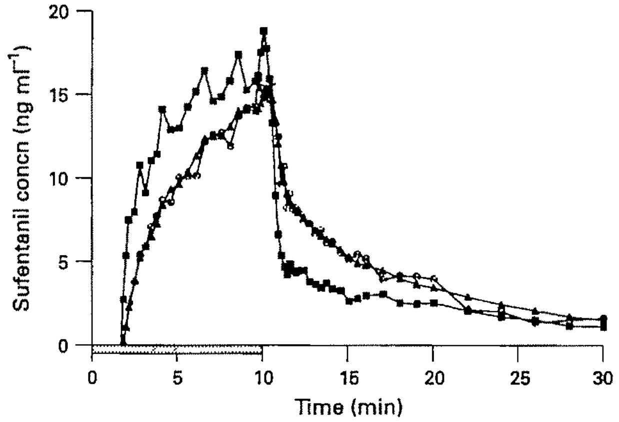


Figure 5 Concentration–time curves of pulmonary arterial concentrations (■), radial arterial concentrations (○) and concentrations predicted from the pulmonary arterial concentrations with the use of physiologically based, two-compartmental pharmacokinetic model (△).

in the first-pass period, considerable recirculation of drug could have occurred before starting pulmonary arterial sampling for the mass balance technique. Cardiac output measurement was infrequent, and the exact timing was not given. We have used a semi-continuous automated thermodilution method, based on system identification analysis [3, 4]. The measurement is semi-continuous, as flow is measured over an epoch period of 45 s and the value presented is the mean of four measurements (i.e. over the last 3 min). Therefore, rapid changes in cardiac output are not observed fast enough to allow correct calculation of the mass balance. However, the changes in blood flow encountered in this study were small as cardiac output decreased gradually to 86 % of initial values over 30 min. Therefore, we feel that the semi-continuous method adequately reflected actual flow.

Mass balance calculation is based on the law of conservation of matter. Mass balance analysis can be applied to the uptake of drugs in an organ or region, if total blood flow feeding that region is known or if flow does not change significantly during the study [2]. Mass balance principles have been used, for instance, to measure uptake and elution of lignocaine and procainamide in the hindquarters of sheep [9]. Use of mass balance principles, however, can be applied only when clear arteriovenous differences are observed. When arteriovenous differences are small compared with the drug assay variability, application of mass balance may yield erroneous results. We have tried to use this method to describe pulmonary retention of alfentanil in a similar patient group. Arteriovenous differences were too small to allow mass balance calculations, because pulmonary retention of alfentanil is small.

The mass balance technique is a model-free method for describing the uptake and release of drug in an organ as a whole. The observed uptake depends on drug characteristics, the method of administration of the drug and the characteristics of the organ or region studied. Because the retention curve depends on the drug input function, the results can only be extrapolated with caution. We have, therefore, also used a non-eliminating, membrane-limited model to describe the pulmonary pharmacokinetics of sufentanil. This model was used assuming that uptake in the lungs is linear with respect to the concentration in the pulmonary artery and that within the flow ranges encountered in this study uptake was not flow-limited. Adding a term for non-linear binding in the model did not improve the prediction of the radial artery concentration curve in these patients, suggesting that binding was linear in our patients. In another study, however, we have shown that first-pass retention of a sufentanil bolus, measured with a double-dilution indication technique, decreased when the background concentration of sufentanil increased [10]. During this study background concentrations of sufentanil increased from 2.8 to 6.9 and 15.9 ng ml^{-1}. First-pass retention of a sufentanil bolus dose was 68 %, 65 % and 60 %, respectively, and retention differed significantly between the lowest and highest background concentrations. The arterial background concentrations in that study were similar to the arterial concentrations encountered in the present study. Possibly sufentanil retention in that study was decreased because sufentanil was given as a bolus. This may have resulted in much higher pulmonary arterial concentrations that those encountered in the present study where sufentanil was given by constant rate infusion.

Table 3 Variables of the physiological based pharmacokinetic model, total volume of distribution and the variables of the system dynamics analysis derived from this model

Patient No.	V_1 (litre)	h (min^{-1})	V_2 (litre)	k_{12} (min^{-1})	k_{21} (min^{-1})	A	$V\mathrm{d}$ (litre)
1	3.1	0.071	20.8	0.023	0.003	0.884	23.9
2	2.9	0.067	19.2	0.023	0.004	0.930	22.1
3	3.1	0.078	25.2	0.026	0.003	0.867	28.3
4	12.4	0.070	19.7	0.006	0.004	1.094	32.1
5	2.4	0.071	9.8	0.029	0.007	0.868	14.2
6	10.8	0.065	15.7	0.006	0.004	1.086	26.5
7	4.1	0.033	12.2	0.008	0.003	1.145	16.3
8	6.6	0.068	17.9	0.010	0.004	1.114	24.5
9	2.9	0.075	10.8	0.026	0.007	1.017	13.7
10	1.6	0.107	7.3	0.069	0.015	0.9318	8.9
Mean	5.0	0.070	15.9	0.023	0.005	0.994	20.9
(SD)	(3.8)	(0.018)	(5.7)	(0.019)	(0.004)	(0.109)	(7.7)

Pulmonary retention of sufentanil at the end of the infusion calculated from the mass balance was higher in smokers. This increased retention did not result in differences in the variables of the pharmacokinetic model used in this study. The reason for the increased retention is unknown. Cigarette smoking is known to significantly change the metabolism of both endogenous and exogenous compounds [11, 12]. However, sufentanil probably undergoes no pulmonary metabolism, as the proportionality constant A of the model was approximately 1. The increased retention can be explained possibly by the increased lipid content in the lungs of smokers. Cigarette smokers are known to have an increased number of alveolar macrophages [13], and these macrophages have an increased lipid content with lipid inclusions, increased lysosomal volume density and secondary lysosomes [14, 15]. It is assumed that the binding of the weak bases to lung tissue may be attributable to a combination of accumulation in membranes and lysosomal trapping [16]. Thus the increase in pulmonary sufentanil retention in smokers might be attributable to an increased binding capacity of the lungs. Compartment analysis did not reveal differences between smokers and non-smokers. Possibly one of the variables V_1, V_2, h or A did not contain enough information on pulmonary retention after a 10-min infusion. The proportionality constant of the model approached unity indicating that no sufentanil was lost in the pulmonary circulation.

Acknowledgement

The computer program used for control of the sampling device was written in Pascal by F. H. M. Engbers, MD (Department of Anaesthesiology, Leiden).

References

1. Boer F, Bovill JG, Burm AGL, Mooren RAG. Uptake of sufentanil, alfentanil and morphine in the lungs of patients about to undergo coronary artery surgery. *British Journal of Anaesthesia* 1992; **68**: 370–375.
2. Upton RN, Mather LE, Runciman WB, Nancarrow C, Carapetis RJ. The use of mass balance principles to describe regional drug distribution and elimination. *Journal of Pharmacokinetics and Biopharmaceutics* 1988; **16**: 13–29.
3. Yelderman ML. Continuous measurement of cardiac output with the use of stochastic system identification techniques. *Journal of Clinical Monitoring* 1990; **6**: 322–332.
4. Yelderman ML, Ramsay MA, Quinn MD, Paulsen AW, McKown RC, Gillman PH. Continuous thermodilution cardiac output measurement in intensive care patients. *Journal of Cardiothoracic and Vascular Anesthesia* 1992; **6**: 270–274.
5. Gilbert HC, Vender JS, Myers P. Evaluation of continuous cardiac output in patients undergoing coronary artery bypass surgery. *Anesthesiology* 1992; **77**: A472.
6. Davis RF, Sakuma G. Comparison of semi-continuous thermodilution to intermittent bolus thermodilution cardiac output determinations. *Anesthesiology* 1992; **77**: A477.
7. Gerlowski LE, Jain RK. Physiological based pharmacokinetic modelling: principles and applications. *Journal of Pharmaceutical Sciences* 1983; **72**: 1103–1127.
8. Taeger K, Weninger E, Schmelzer F, Adt M, Franke N, Peter K. Pulmonary kinetics of fentanyl and alfentanil in surgical patients. *British Journal of Anaesthesia* 1988; **61**: 425–434.
9. Upton RN, Runciman WB, Mather LE, McLean CF, Ilsley AH. The uptake and elution of lignocaine and procainamide in the hindquarters of the sheep described using mass balance principles. *Journal of Pharmacokinetics and Biopharmaceutics* 1988; **16**: 31–40.
10. Boer F, Engbers FHM, Bovill JG, Burm AGL, Hak A. Sufentanil first-pass pulmonary uptake at three different steady state concentrations of the drug. *British Journal of Anaesthesia* 1995; **74**: 50–55.
11. Bahkle YS, Hartiala J, Toivonen H, Uotila P. Effects of cigarette smoke on the metabolism of vasoactive hormones in rat isolated lungs. *British Journal of Pharmacology* 1979; **65**: 495–499.
12. Kitamura S. Effects of cigarette smoking on metabolic events in the lungs. *Environmental and Health Perspectives* 1987; **72**: 283–296.
13. Hoidal JR, Niewoehner DE. Lung phagocyte recruitment and metabolic alterations induced by cigarette smoke in humans and in hamsters. *American Review of Respiratory Disease* 1982; **126**: 548–552.
14. Harris JO, Swenson EW, Johnson JE. Human alveolar macrophages: comparison of phagocyte ability, glucose utilization, and ultrastructure in smokers and nonsmokers. *Journal of Clinical Investigation* 1970; **49**: 2086–2096.
15. Davies P, Sornberger GC, Huber GL. The stereology of pulmonary alveolar macrophages after prolonged experimental exposure to tobacco smoke. *Laboratory Investigation* 1977; **37**: 297–306.
16. MacIntyre AC, Cutler DJ. The potential role of lysosomes in tissue distribution of weak bases. *Biopharmaceutics and Drug Disposition* 1988; **9**: 513–526.

British Journal of Anaesthesia 1996; **76**: 209–213

Does pre-incisional thoracic extradural block combined with diclofenac reduce postoperative pain after abdominal hysterectomy?

A. ESPINET, D. J. HENDERSON, K. A. FACCENDA AND L. M. M. MORRISON

Summary

In a double-blind, randomized study, we investigated 40 patients undergoing abdominal hysterectomy; patients received 0.5% plain bupivacaine 20 ml via a low thoracic extradural catheter and a diclofenac suppository (100 mg), either 30 min before incision (group 1) or 30 min after incision (group 2). All patients received a standard general anaesthetic and no opioid was used before or during operation. Postoperative analgesic requirements were measured using a patient-controlled analgesia (PCA) system. Pain was assessed using a visual analogue scale (VAS) and a verbal pain score (VPS) on movement up to 48 h after operation. There was no significant difference in the time to first request for morphine but consumption of morphine was significantly greater in group 1 at all times except 24 h. There were no significant differences in VAS and VPS pain scores, although both scores were consistently higher in group 1. Patient satisfaction with the quality of analgesia, at 24 h, demonstrated no significant difference between the two groups. The combination of extradural block and diclofenac suppository given before operation did not appear to produce a clinically effective pre-emptive analgesic effect. (*Br. J. Anaesth.* 1996; **76**: 209–213)

Key words

Anaesthetic techniques, extradural. Analgesia, pre-emptive. Pain, postoperative. Surgery, gynaecological.

Recent developments in the field of neurophysiology have led to greater understanding of the pathophysiology of acute pain and wider acceptance of the concept of neuroplasticity. The evidence for this concept relies largely on laboratory studies [1, 2] which have demonstrated that peripheral tissue injury may induce long lasting changes in the central nervous system and a state of hyperexcitability (CNS "wind up"). Further stimuli are then thought to potentiate these neural impulses and so generate or intensify pain [3]. Studies with animals have shown that noxious stimulus-induced neuroplasticity can be reduced or prevented (i.e. pre-empted) by pre-injury neural block with local anaesthesia [4, 5], or by administration of opioids i.v. [2] or intrathecally [6]. In addition to this central mechanism of pain production, peripheral sensitization may occur with tissue trauma and lead to pain [7]. Injury may sensitize nociceptors and cause primary hyperalgesia at the site of injury and secondary hyperalgesia in the undamaged tissue surrounding the injury. The mechanisms for this may include release of multiple inflammatory mediators, and other chemicals liberated by, or in reaction to, tissue damage [8, 9]. In order to influence this peripheral pathway, some researchers have used preoperative non-steroidal anti-inflammatory agents (NSAID) and have reported a reduction in postoperative pain [10, 11]. Taken together, these studies would suggest that the use of a combined technique such as local anaesthetic administered centrally and an anti-inflammatory drug (NSAID) peripherally, may reduce postoperative pain and analgesic requirements.

The aim of our study was to evaluate the efficacy of pre-emptive analgesia by combining NSAID and extradural block with local anaesthesia given either before or after surgical incision. Our hypothesis was that if we pre-empted both the central and peripheral sensitization of the nervous system, then patients receiving the pre-incisional analgesic combination would report a lower pain intensity and consume smaller quantities of analgesics after operation, than a similar group given the same combination after incision.

Patients and methods

Over a 6-month period, we studied 40 women, aged 30–60 yr, ASA I or II, undergoing elective abdominal hysterectomy, after obtaining informed consent and approval of the local Ethics Committee. Patients were excluded if there was any history or evidence of back pain, or other chronic pain condition, any contraindication to the use of extradural block, bupivacaine or halothane, regular intake of analgesic drugs, morbid obesity or a psychiatric history.

All patients were premedicated with temazepam 10–20 mg, 60–90 min before operation. Before induction of general anaesthesia, a low thoracic

---

A. ESPINET*, BSC, MBBS, FRCA, D. J. HENDERSON*, MB, CHB, K. A. FACCENDA, MB, CHB, FRCA, L. M. M. MORRISON, BSC, MB, CHB, FFARCSI, Department of Anaesthetics, St John's Hospital at Howden, Howden Road West, Livingston EH54 6PP. Accepted for publication: September 5, 1995.

*Present address: Department of Anaesthetics, Royal Infirmary of Edinburgh.

Correspondence to L.M.M.M.

extradural catheter (T9–12) was sited by one of the authors in a standard manner, using an 18-gauge Tuohy needle. The catheter was flushed with normal saline. No test dose of local anaesthetic was given. The 40 patients were allocated randomly using a numbers table to one of two equal groups. Group 1 received 0.5 % plain bupivacaine 20 ml as a "single shot" and a suppository of diclofenac 100 mg, 30 min before incision. Group 2 received 0.5 % plain bupivacaine 20 ml, 30 min after surgical incision and the diclofenac suppository immediately after surgery. Bupivacaine was administered in a standard manner while observing for signs of toxicity. Adequacy of analgesia (to at least the T10 dermatomal level bilaterally) was assessed with ethyl chloride spray to confirm the height of the block, either before commencement of general anaesthesia (group 1) or on awakening at the end of operation (group 2). Any patient with an inadequate block (i.e. not pain free) was eliminated from the study (one patient from each group). General anaesthesia was induced with a sleep dose of propofol, and neuromuscular block was produced with atracurium. The trachea was intubated and the lungs ventilated with oxygen–air and halothane 1.0–1.5 MAC in order to maintain anaesthesia. The end-tidal carbon dioxide partial pressure was maintained within the normal range (4.5–5.5 kPa). Neuromuscular block was monitored with a peripheral nerve stimulator, and increments of atracurium given as indicated. At the end of the operation residual neuromuscular blockade was antagonized with neostigmine 2.5 mg and atropine 1.2 mg and this time was taken as time "0". Assessment of postoperative pain on movement (from supine to sitting), was made at 2, 4, 6, 12, 24 and 48 h using a 10-cm visual analogue scale (VAS) (0 = no pain, 10 = worst pain imaginable).

A simple four-point verbal pain score (VPS) was also used (0 = no pain at rest or movement, 1 = no pain at rest, slight pain on movement; 2 = intermittent pain at rest, moderate pain on movement; 3 = continuous pain at rest, severe pain on movement). These assessments were made by an independent observer who was blinded to the timing of the extradural block. Postoperative analgesic requirements were measured using a patient-controlled analgesia (PCA) system (Graseby 3300). This was programmed to deliver a 1-mg bolus of morphine with a 5-min lockout and no background infusion. PCA morphine was used for a maximum period of 24 h, after which the patient received diclofenac suppositories or oral codydramol on request. Patient satisfaction with the quality of the analgesia was assessed at 24 h as one of five responses: 1 = very dissatisfied, 2 = dissatisfied, 3 = satisfied, 4 = happy and 5 = very happy.

STATISTICAL ANALYSIS

Before the start of the study, we estimated the sample size required to test the hypothesis that postoperative pain would be less in group 1 than in group 2. Based on previous research at our institution using the same surgical population and the same outcome measure (i.e. VAS for postoperative pain), estimates of the effect size and variance were used to calculate the sample size ($n = 20$ per group) required to give the study a power of 0.9 (and a type 1 error rate of 0.05). The cumulative morphine dose, VAS and VPS pain scores were compared between the two groups at the designated times using the Mann–Whitney test with Bonferroni's type 1 error rate correction for multiple tests of significance. Data are presented as median (quartiles or range). $P < 0.05$ was considered statistically significant for all tests.

Results

Both groups were similar in age, weight and height (table 1). In both groups the duration of surgery was less than 60 min.

The time from the end of surgery to first use of morphine did not differ significantly between the pre-incision (median time 120 (range 30–600) min) and post-incision (120 (60–420) min groups. Morphine consumption was consistently greater in group

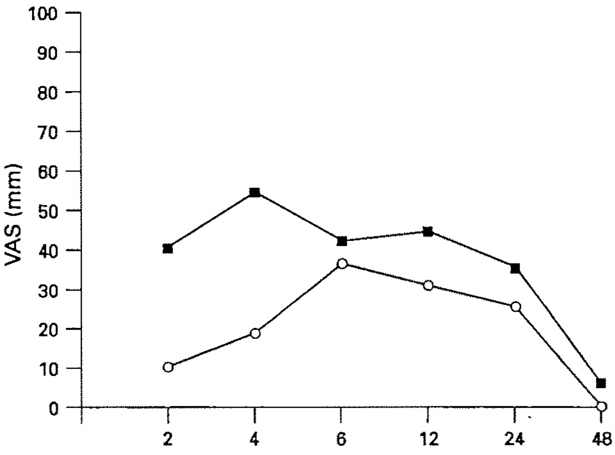


Figure 1 Visual analogue scale (VAS) for pain or movement (median) in groups 1(■) and 2 (○).

Table 1 Patient data (mean (range))

	Group 1 ($n = 19$)	Group 2 ($n = 19$)
Age (yr).. .	41.1 (30–52)	43.2 (33–52)
Height (cm)	166 (155–180)	160.9 (152–170)
Weight (kg)	72.5 (57–89)	64.8 (47–90)

Table 2 Morphine consumption (mg) (median (quartiles))

	Time (h)				
	2	4	6	12	24
Group 1	5 (2–14)	10 (7–25.5)	17 (9.75–36)	32.5 (20.5–51.5)	42 (31–70)
Group 2	1 (0–6.5)	3 (1.75–10)	8.5 (3.75–16.25)	18.5 (14–28.5)	34.5 (19–46)

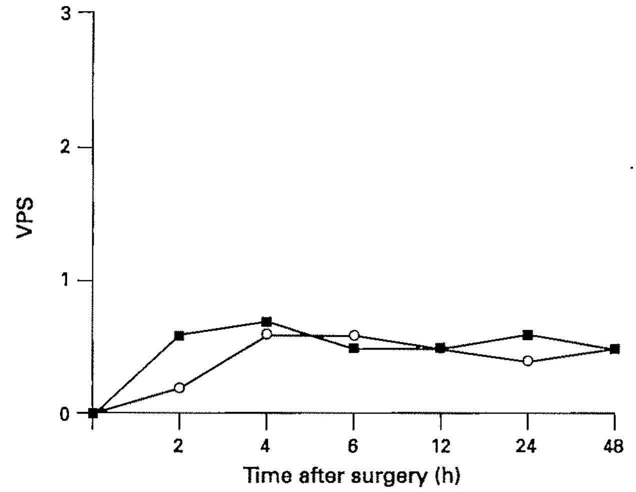


Figure 2 Verbal pain score (VPS) on movement (median) in groups 1 (■) and 2 (○).

1 than in group 2 and this was significant ($P < 0.05$) at all times, except 24 h (table 2). The patients were followed-up for 48 h after surgery and there was no difference in time to discontinuation of the PCA pump or in subsequent analgesic requirements (diclofenac and codydramol), between the two groups.

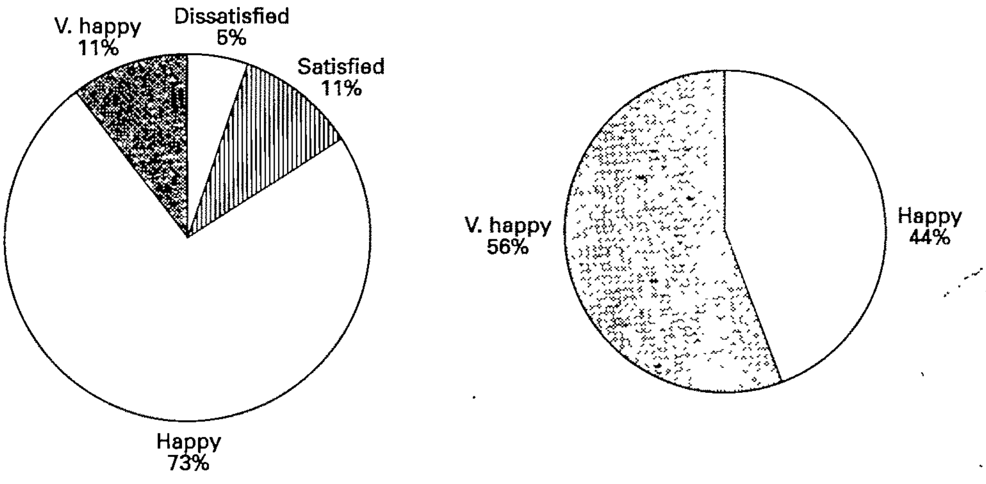
There were no statistically significant differences in VAS and VPS pain scores (figs 1, 2). Patient satisfaction, assessed at 24 h, revealed no significant difference between the two groups (group 1, median score 4 (happy); group 2, median score 5 (very happy)) (fig. 3).

Discussion

Our study failed to show any clinical benefit either in terms of postoperative pain, analgesic requirements or overall patient satisfaction in the group of patients receiving extradural block and diclofenac suppository before, compared with after, surgical incision. A trend was observed in group 1 towards higher postoperative pain scores, higher morphine consumption and lower overall patient satisfaction, suggesting that other factors are important in the pathophysiology of pain after the extensive trauma of major surgery, which may not be applicable in the experimental situation.

Other centres investigating the possible clinical role of pre-emptive analgesia have confirmed our findings. Orntoft and colleagues [12], in a well-controlled, double-blind study, compared pre- and postoperative tonsillar infiltration with bupivacaine and found no beneficial pre-emptive analgesic effect from preoperative infiltration. Pryle and colleagues [13] performed a lumbar extradural block before or after incision to women undergoing abdominal hysterectomy or myomectomy. They failed to demonstrate any pre-emptive benefit on postoperative pain. However, their results may be criticized because both groups received opioid premedication and nitrous oxide was used. Dierking and co-workers [14], using an inguinal field block before or after hernia repair, were unable to demonstrate any difference in either immediate or late postoperative pain. Unfortunately, both groups were given alfentanil i.v. at induction and again during the procedure, and this may have influenced the outcome. Dahl and colleagues [15] studied the effect of continuous extradural analgesia (with bupivacaine and morphine) given before and after major abdominal surgery. They found no significant differences between the two groups in terms of pain scores and analgesic requirements. Again, their results may have been influenced by the fact that in both groups a test dose of bupivacaine was given to confirm correct placement of the catheter, i.v. fentanyl was given at induction and nitrous oxide was used for maintenance of anaesthesia.

Many of the studies which have claimed support for the concept of pre-emptive analgesia have also been flawed because they were either poorly designed [16], retrospective [17], uncontrolled [18, 19] or, when repeated, failed to produce similar results [12, 20]. Pre-emptive analgesic effects have been demonstrated with the use of preoperative and intra-operative opioids (i.v. [6, 21], i.m. [18] and extradural [22]), local anaesthetic test doses [23],



Group 1 ($n = 19$) Group 2 ($n = 18$)

Figure 3 Patient satisfaction 24 h after operation in both groups.

and with the use of nitrous oxide [24]. We designed our study in order to avoid these confounding factors.

The concept of pre-emptive analgesia is an attractive one because, if proved in the clinical setting, it may protect patients from the deleterious effects of surgical incision and other noxious perioperative events long after the operation has been performed. Taken further, the notion of painless surgery presents as a distinct possibility. Clear clinical evidence for pre-emptive analgesia however, has yet to be established, despite what appears to be convincing experimental evidence [1, 2, 4, 5, 25]. Much of the initial work supporting this concept of "pain prevention" originates from animal studies [1, 26], which have demonstrated that under specific conditions in the experimental model, noxious impulses generated by localized peripheral tissue trauma can lead to sensitization of the central nervous system (CNS) and enhancement of painful stimuli thereafter. Preventing these impulses from reaching the CNS can significantly reduce the post-injury hypersensitivity to pain. The exact mechanism for this "wind-up" phenomenon awaits further elucidation, but recent evidence suggests that C-fibre excitatory amino acids and neuropeptides are involved [26]. These may be operating through activation of *N*-methyl-D-aspartate (NMDA) receptors [27] in the short term, but other molecular changes and new gene expression [28, 29] may also play a role in the longer term hyperaesthesia and allodynia.

In the clinical environment, however, other factors may be involved in the production of postoperative pain. For example, surgical trauma differs from the stimuli used in experimental models, in that the afferent input to the CNS during surgery may be extensive, involving mixed cutaneous, muscular and visceral components. The degree of surgical trauma and the site of operation are also important in influencing the amount of nociceptive input. Kehlet's work [30] has shown that complete block of these noxious stimuli during surgery is difficult, unless an extensive extradural block from T4 to S5 is obtained. In addition, persistent inflammation and hyperalgesia at the wound site [14] may generate C-fibre activity well into the postoperative period. In some instances, the magnitude of the injury sustained by the tissues may be comparable with that occurring in the experimental situation. If so, the pre-emptive interventions used are able to produce the dramatic differences between groups of patients reported [31, 32], as has been demonstrated in the animal model. These factors may in part be responsible for the conflicting results of the many clinical studies reported.

References

1. Woolf CJ. Evidence for a central component of postinjury pain hypersensitivity. *Nature (London)* 1983; **306**: 686–688.
2. Woolf CJ, Wall PD. Morphine sensitive and morphine insensitive actions of C-fibre input on rat spinal cord. *Neuroscience Letters* 1986; **64**: 221–225.
3. Wall PD. The prevention of postoperative pain. *Pain* 1988; **33**: 289–290.
4. Coderre TJ, Melzack R. Cutaneous hyperanalgesia: contributions of the peripheral and central nervous systems to the increase in pain sensitivity after injury. *Brain Research* 1987; **404**: 95–106.
5. Coderre TJ, Vaccarino AL, Melzak R. Central nervous system plasticity in the tonic pain response to subcutaneous formalin injection. *Brain Research* 1990; **535**: 155–158.
6. Dickenson AH, Sullivan AF. Subcutaneous formalin induced activity of dorsal horn neurones in the rat: differential response to an intrathecal opiate administered pre or post formalin. *Pain* 1987; **30**: 349–360.
7. Lamotte RL, Thalhammer JG, Torebjork HE, Robinson CJ. Peripheral neural mechanisms in cutaneous hyperalgesia following mild injury by heat. *Journal of Neuroscience* 1982; **2**: 765–781.
8. Treede RD, Meyer RA, Raja SN, Campbell JN. Peripheral and central mechanisms of cutaneous hyperalgesia. *Progress in Neurobiology* 1992; **38**: 397–421.
9. Rang HP, Bevan S, Drag A. A chemical activation of nociceptive peripheral neurones. *British Medical Bulletin* 1991; **47**: 534–538.
10. Owen J, Glavin RJ, Shaw NA. Ibuprofen in the management of postoperative pain. *British Journal of Anaesthesia* 1986; **58**: 1371–1375.
11. Campbell WI, Kendrick R. Intravenous diclofenac sodium. Does its administration before operation suppress postoperative pain? *Anaesthesia* 1990; **45**: 763–766.
12. Orntoft S, Longreen A, Moiniche S, Dahl JB. A comparison of pre- and postoperative tonsillar infiltration with bupivacaine on pain after tonsillectomy: a pre-emptive effect? *Anaesthesia* 1994; **49**: 151–154.
13. Pryle BJ, Vanner RG, Enriquez N, Reynolds F. Can pre-emptive epidural blockade reduce postoperative pain following lower abdominal surgery? *Anaesthesia* 1993; **48**: 120–123.
14. Dierking GW, Dahl JB, Kangstrup J, Dahl A, Kehlet H. Effect of pre and postoperative inguinal field block on postoperative pain after herniorrhaphy. *British Journal of Anaesthesia* 1992; **68**: 344–348.
15. Dahl JB, Hansen BL, Hjortso NC, Erichsen CJ, Moiniche S, Kehlet H. Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery. *British Journal of Anaesthesia* 1992; **69**: 4–8.
16. McQuay HJ. Pre-emptive analgesia. *British Journal of Anaesthesia* 1992; **69**: 1–3.
17. McQuay HJ, Carroll D, Moore RA. Postoperative orthopaedic pain: The effect of opiate premedication and local anaesthetic blocks. *Pain* 1988; **33**: 291–295.
18. Kiss IE, Kilian M. Does opiate premedication influence postoperative analgesia? A prospective study. *Pain* 1992; **48**: 157–158.
19. Agrewn K, Engquist S, Dannemann A, Feychting B. Local versus general anaesthesia in tonsillectomy. *Clinical Otolaryngology* 1989; **14**: 97–100.
20. Ejlersen E, Bryde-Anderson MD, Elisen K, Mogensen T. A comparison between preincisional and postincisional lidocaine infiltration and postoperative pain. *Anesthesia and Analgesia* 1992; **74**: 495–498.
21. Richmond CE, Bromley LM, Woof CJ. Preoperative morphine preempts postoperative pain. *Lancet* 1993; **342**: 73–75.
22. Katz J, Kavanagh BP, Sandler AN, Nierenberg H, Boylan JF, Friedlander M, Shaw BF. Pre-emptive analgesia: clinical evidence of neuroplasticity contributing to postoperative pain. *Anesthesiology* 1992; **77**: 439–446.
23. Katz J, Kavanagh BP, Clairoux M, Sandler AN. Pre-emptive analgesia. *British Journal of Anaesthesia* 1993; **70**: 378.
24. Katz J. Preop analgesia for postoperative pain. *Lancet* 1993; **342**: 65–66.
25. Woolf CJ, Chong MS. Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitisation. *Anesthesia and Analgesia* 1993; **77**: 362–379.
26. Cook AJ, Woolf CJ, Wall PD. Prolonged C-fibre mediated facilitation of the flexion reflex is not due to changes in afferent terminal or motoneurone excitability. *Neuroscience Letters* 1986; **70**: 91–96.
27. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitisation is dependent on N-methyl-D aspartic acid receptor activation: implications for the treatment of

post-injury pain hypersensitivity states. *Pain* 1991; **44**: 293–299.

28. Hunt SP, Pini A, Evan G. Induction of c-fos like protein in spinal cord neurones following sensory stimulation. *Nature (London)* 1987; **328**: 632–634.
29. Morgan JI, Curran T. Stimulus–transcription coupling in neurons: role of cellular immediate-early genes. *Trends in Neurosciences* 1989; **12**: 459–462.
30. Kehlet H. Modification of responses to surgery by neural blockade: clinical complications. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anaesthesia and Management of Pain,* 2nd Edn. Philadelphia: JB Lippincott, 1983; 145–188.
31. Tverskoy M, Cozacov C, Ayache M, Bradley EL, Kissin I. Postoperative pain after inguinal herniorrhaphy with different types of anesthesia. *Anesthesia and Analgesia* 1990; **70**: 29–35.
32. Jebeles JA, Reilly JS, Guitierrez JF, Bradley EL, Kissin I. The effect of preincisional infiltration of tonsils with bupivacaine on the pain following tonsillectomy under general anaesthesia. *Pain* 1991; **47**: 305–308.

British Journal of Anaesthesia 1996; **76**: 214–220

Influence of oral clonidine on the ventilatory response to acute and sustained isocapnic hypoxia in human males†

I. T. FOO, P. M. WARREN AND G. B. DRUMMOND

Summary

Animal studies suggest that α_2 agonists inhibit the chemoreceptor response to hypoxia. We have examined the effect of oral clonidine on the ventilatory response to sustained, isocapnic hypoxia (Sp_{O_2} 79.7% (SD 1.1 %) for 20 min) in eight male subjects. The hypoxic ventilatory response was measured before and after both clonidine and placebo. Clonidine had no significant effect on baseline ventilation or gas exchange. After clonidine, the acute hypoxic response (AHR) (mean 5.81 (95% confidence limits 1.94, 9.68) litre min^{-1}) was significantly less than control (10.40 (5.97, 14.83) litre min^{-1}) and hypoxic ventilatory decline (HVD) (3.42(2.35, 4.49) litre min^{-1}) was also significantly less than control (6.49(3.92, 9.06) litre min^{-1}) ($P < 0.05$). After placebo, AHR was similar to control but HVD was significantly larger (6.82(5.28, 8.36) litre min^{-1}) than control (4.79(3.03, 6.55) litre min^{-1}) ($P < 0.05$). Thus clonidine reduced both AHR and HVD but the absolute level of ventilation at the end of hypoxia was unchanged. (*Br. J. Anaesth.* 1996; **76**: 214–220)

Key words

Hypoxia. Ventilation, hypoxic response. Pharmacology, clonidine. Sympathetic nervous system, clonidine.

Clonidine, and more recently the highly selective α_2 adrenoceptor agonist dexmedetomidine, are used as adjuncts to general anaesthesia. They cause sedation and anxiolysis before operation, reduce haemodynamic responses, anaesthetic and analgesic requirements during operation, and reduce opioid requirements after operation [1].

The influence of α_2 agonists on respiration is uncertain. Some clinical studies have suggested that clonidine causes no or only minimal ventilatory depression [2, 3], whereas others have shown a reduction in the slope of the hypercapnic ventilatory response when clonidine was given i.v. [4] or extradurally [5]. Furthermore, episodes of arterial oxygen desaturation have occurred in association with abnormal ventilatory patterns after oral and extradural clonidine [6, 7].

α_2 Adrenergic receptors are present in the cat carotid body and they inhibit the chemoreceptor response to hypoxia [8]. Consequently, the ventilatory response to hypoxia could be attenuated by α_2 agents and thus cause more hypoxaemia in susceptible patients. However, dexmedetomidine did not affect the hypoxic ventilatory response in dogs, even at high doses [9]. Species differences may account for the discrepancy and extrapolation of animal results to humans may be inappropriate. Because of these uncertainties and as no human data are available, we have studied the effects of oral clonidine on the ventilatory response to sustained, isocapnic hypoxia in humans.

Subjects and methods

We studied 10 healthy male volunteers, none of whom was a smoker, had a history of cardiorespiratory disease or was receiving medication at the time of study. Subjects were asked to refrain from taking substances known to affect respiration (e.g. caffeine, chocolate, etc.) for a minimum of 6 h before the study and were studied after fasting for 4 h. Local Ethics Committee approval was obtained and all subjects gave written informed consent.

Each subject attended the laboratory on three occasions. The first visit was a familiarization period. A medical history was obtained and FEV_1 and FVC measurements were taken to assess and confirm normal lung function. The ventilatory response to 20 min of sustained hypoxia (Sp_{O_2} 80 %) was then measured. Each of the other 2 study days consisted of an initial control hypoxic run, followed by a further hypoxic run 1 h after either oral clonidine (approximately 3.5 μg kg^{-1} rounded up to the nearest 50 μg) or matched placebo tablets. During the 1 h wait between runs, subjects were seated in a waiting room and allowed to read. At the end of each hypoxic run, manual measurement of lying and standing arterial pressures were recorded (mercury sphygmomanometer using Korotkoff IV as end-point). To minimize the effects of diurnal variation on the hypoxic ventilatory response, studies on each subject were always scheduled for the same time of day. Neither the subject nor the assessor of ventilatory variables was aware of the treatment received.

I. T. FOO*, BSC(HONS), MB, BCHIR, MRCP(UK), FRCA, G. B. DRUMMOND, MA, MB, CHB, FRCA (Department of Anaesthetics); P. M. WARREN, BSC, PHD (Rayne Laboratory, Unit of Respiratory Medicine, Department of Medicine); Royal Infirmary, Edinburgh, University of Edinburgh, Edinburgh. Accepted for publication: September 28, 1995.

*Address for correspondence: Department of Anaesthetics, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW.

†Presented in part at the Anaesthetic Research Society, Leeds Meeting, March 31–April 1, 1995 (*British Journal of Anaesthesia* 1995; 75: 232P–233P).

The methods used for recording ventilatory variables have been described previously [10]. Briefly, subjects were seated upright in a comfortable armchair in a well-lit room and breathed via a mouthpiece and noseclip arrangement through a low resistance two-way valve. A five-way valve (Hans-Rudolf Gatlin Valve series 2430) was connected to the inspiratory port of the two-way valve to allow changes in inspired gases without the subject's knowledge. Expiratory gas passed via a heated pneumotachograph (Fleisch No. 2) through mixing and drying chambers to a Parkinson Cowan CD4 dry gas meter modified to give a digital signal. The integrated expiratory flow signal, which gave breath-by-breath tidal volume, was calibrated against the output of the CD4 gas meter every 10 litre to correct the flow signal. Inspiratory and end-tidal oxygen ($P\mathrm{I}_{O_2}$, $P\mathrm{E}'_{O_2}$) and carbon dioxide ($P\mathrm{I}_{CO_2}$, $P\mathrm{E}'_{CO_2}$) partial pressures were measured at the lips via a mass spectrometer (VG Spectralab M). Pulse oximetry ($S\mathrm{p}_{O_2}$) (Ohmeda Biox 3700, set to a fast averaging time of 2 s) and electrocardiogram (Hewlett-Packard 78351A) were measured continuously throughout the study.

Breath-by-breath values of inspiratory time ($T\mathrm{I}$, s), expiratory time ($T\mathrm{E}$, s), total breath time ($T\mathrm{Tot} = T\mathrm{I} + T\mathrm{E}$, s), ventilatory frequency ($f = 60/T\mathrm{Tot}$, b.p.m.), tidal volume ($V\mathrm{T}$, litre, BTPS), instantaneous minute ventilation ($\dot{V}\mathrm{E}^{\mathrm{inst}} = f \times V\mathrm{T}$, litre, BTPS), mean inspiratory flow ($V\mathrm{T}:T\mathrm{I}$, litre s^{-1}), inspiratory time:total breath time ratio ($T\mathrm{I}:T\mathrm{Tot}$), $S\mathrm{p}_{O_2}$ (%), inspired and end-tidal partial pressures were digitized using a DEC PDP 11/23 computer and stored on disk for off-line analysis. Oxygen consumption ($\dot{V}O_2$, litre min^{-1}, STPD) and carbon dioxide output ($\dot{V}CO_2$, litre min^{-1}, STPD) were measured from collections of mixed expired gas made over 2-min periods and the gas exchange ratio calculated (R). During each run subjects listened to music through headphones and were asked to remain awake. Subjects were aroused by an observer if they appeared to be asleep.

Measurements were made with the subjects seated at rest. Initially, room air was breathed for 15 min and duplicate measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ were made between 5 and 10 min. $S\mathrm{p}_{O_2}$ was then reduced to approximately 80 % for 20 min. To achieve a square wave response, subjects were initially given two breaths of 100 % nitrogen followed by an inspired oxygen concentration of approximately 10 %. At the end of hypoxia, subjects were given one breath of 100 % before returning to 5 min of room air. All changes in gas concentrations were made during expiration. During hypoxia, carbon dioxide was added to the inspired gas to maintain $P\mathrm{E}'_{CO_2}$ as close as possible to the baseline normoxic value. Each session lasted 40 min.

Mean values for each minute for all measured ventilatory variables were calculated for each subject. In addition, mean values during the following four measurement periods of each run were calculated: baseline normoxia (A1: 4 min immediately before the onset of hypoxia); early hypoxia (H1: minutes 3–6 inclusive of hypoxia); late hypoxia (H2: minutes 17–20 inclusive of hypoxia); and normoxic recovery (A2: minutes 2–5 inclusive after return to breathing room air). Three further variables were derived: the acute hypoxic ventilatory response (AHR) was calculated as the difference between periods A1 and H1, the absolute magnitude of the decline in ventilation during sustained hypoxia (HVD) was calculated as the difference in ventilation between periods H1 and H2, and the off-response was calculated as the difference in ventilation between periods H2 and A2.

Group means and SD for imposed respiratory variables and group means and confidence limits (CL) for studied respiratory variables in the four measurement periods, including the three derived variables, were calculated for each run. Within a run, the respiratory variables in the four measurement periods were subjected to one-way analysis of variance with *post hoc* multiple comparisons with the Scheffé test. Both placebo and clonidine runs were compared with their respective control runs using the Student's paired t test. $P < 0.05$ was taken as significant. All computations were carried out using the SPSS for Windows version 6 statistical package, run within MS DOS 6.2.

Results

All subjects completed both study days. All reported a dry mouth and drowsiness after clonidine but all remained awake during the hypoxic runs. Moderate bradycardia (40–50 beat min^{-1}) and postural hypotension were observed in the majority of subjects after clonidine but none required any intervention.

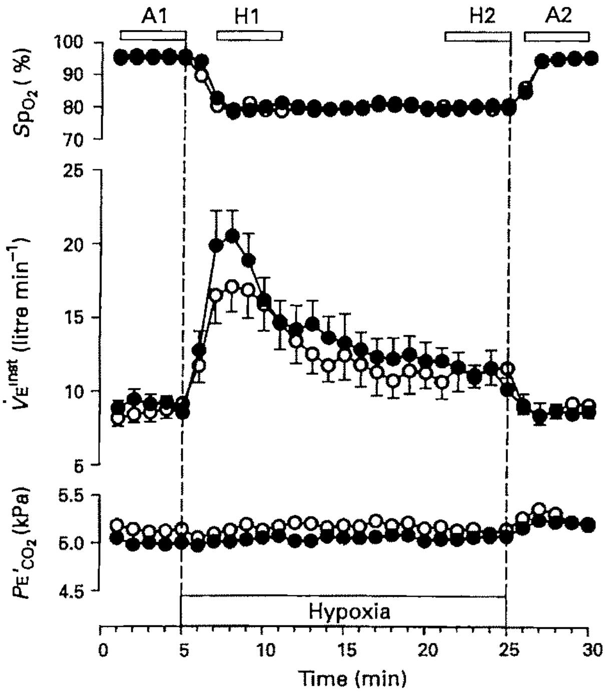


Figure 1 Oxygen saturation ($S\mathrm{p}_{O_2}$), instantaneous minute ventilation ($\dot{V}\mathrm{E}^{\mathrm{inst}}$) and $P\mathrm{E}'_{CO_2}$ plotted against time for control (○) and placebo (●) runs. Mean values for each 1-min period are presented. For clarity, SEM presented only for $\dot{V}\mathrm{E}^{\mathrm{inst}}$. Mean values for each variable were calculated over the periods A1 (baseline normoxia), H1 (early hypoxia), H2 (late hypoxia) and A2 (normoxic recovery) for each subject and used for comparison between run.

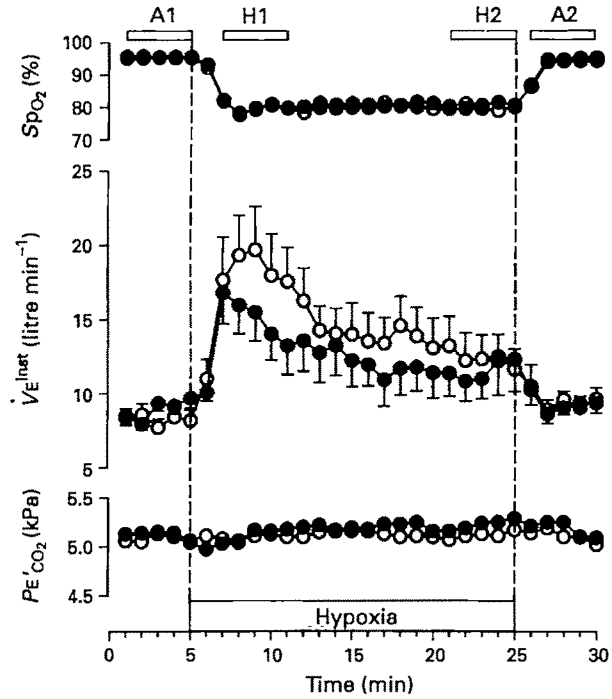


Figure 2 Oxygen saturation (Sp_{O_2}), instantaneous minute ventilation ($\dot{V}E^{inst}$) and PE'_{CO_2} plotted against time for control (○) and clonidine (●) runs. Mean values for each 1-min period are presented. For clarity, SEM presented only for $\dot{V}E^{inst}$. Periods as in figure 1.

Of the 10 subjects recruited, two appeared to develop obstructive breathing patterns after clonidine during the hypoxic phase of the run which would have made analysis of ventilatory variables difficult. We decided therefore, before analysis of the results, to eliminate the data from these two subjects, leaving eight subjects for analysis. The remaining subjects had a mean age of 34 (range 26–50) yr, mean height of 1.80 (1.64–1.92) m and mean weight of 81.7 (73.0–96.0) kg.

The pattern of ventilatory response to hypoxia was similar in all four runs (both control runs, after placebo and after clonidine) with an initial brisk increase in ventilation followed by a slower decline to a plateau (figs 1, 2). Within runs, there were no significant differences in PE'_{CO_2} for the four measurement periods or for PE'_{O_2} and Sp_{O_2} for both H1 and H2 measurement periods. Sp_{O_2} was reduced to approximately 80% during hypoxia, and PE'_{CO_2} was controlled, on average, to within 0.07 kPa of baseline normoxic values during hypoxia.

After placebo, $\dot{V}O_2$, $\dot{V}CO_2$ and respiratory quotient did not differ significantly compared with the control (table 1). Imposed variables were similar for the four measurement periods, except for very small but significant differences in Sp_{O_2} and PE'_{CO_2} during normoxic baseline and early hypoxia compared with the preceding control (table 2). After placebo, there were no significant differences in ventilatory variables, except for *f* which was significantly greater during early hypoxia, and *V*T which was significantly less during normoxic recovery. AHR did not differ between placebo and its control but HVD was significantly reduced after placebo. No significant difference between placebo and control was detected in the off-response (table 3).

After clonidine, $\dot{V}O_2$, $\dot{V}CO_2$ and respiratory quotient were not statistically different compared with the control (table 1). Imposed variables were similar for the four measurement periods, except for very small but significant differences in Sp_{O_2} during early hypoxia and PE'_{CO_2} during late hypoxia compared with the preceding control (table 4). There were no significant differences in ventilatory variables after clonidine during either normoxic baseline or recovery. After clonidine, $\dot{V}E^{inst}$, *V*T and *V*T : *T*I were significantly less during early hypoxia compared with control but there was no difference in *f*. In contrast, during late hypoxia, *f* was significantly less after clonidine but there were no significant differences in all other ventilatory variables (table 4). Both AHR and HVD were reduced significantly compared with control after clonidine. The off-response was not significantly different after clonidine (table 3).

Discussion

We have demonstrated in normal male subjects that oral clonidine, in doses used for premedication, significantly reduced the initial increase in ventilation during hypoxia but did not affect final ventilation when hypoxia was sustained for 20 min. The reduction in ventilation by clonidine during early hypoxia was caused by a reduction in *V*T with no change in *f*. This was reflected in the reduction in *V*T : *T*I which suggests an effect on respiratory drive. After placebo, ventilation was not significantly different from the preceding control run, suggesting no order effect.

We did not study females in this study because their hypoxic ventilatory response is affected by varying plasma progestogen concentrations during the menstrual cycle [11]. Consequently, studies would have had to be scheduled according to the menstrual cycle and this was impractical for volunteers. However, there is no obvious reason why the general findings do not apply to women.

Studies were conducted on 2 separate days because the long elimination half-life of clonidine [12] did

Table 1 Mean (95% confidence limits) baseline normoxic values for gas exchange during the control and treatment runs. No significant differences between treatment (placebo or clonidine) and respective control runs

	$\dot{V}O_2$ (ml min^{-1})	$\dot{V}CO_2$ (ml min^{-1})	Gas exchange ratio
Control	269 (230, 308)	239 (209, 269)	0.90 (0.86, 0.94)
Placebo	260 (227, 293)	238 (204, 273)	0.92 (0.86, 0.97)
Control	270 (231, 309)	235 (193, 278)	0.87 (0.82, 0.91)
Clonidine	257 (221, 293)	220 (191, 248)	0.86 (0.80, 0.92)

Table 2 Mean (SD) imposed ventilatory variables and mean (95 % confidence limits) studied ventilatory variables in the four measurement periods for control and placebo runs. $^*P < 0.05$ compared with control

	Normoxia baseline	Early hypoxia	Late hypoxia	Normoxia recovery
Imposed variables				
$P\text{E}'_{CO_2}$ (kPa)				
Control	5.13 (0.24)	5.15 (0.23)	5.13 (0.21)	5.28 (0.24)
Placebo	4.99 (0.27)*	5.04 (0.27)*	5.06 (0.30)	5.23 (0.28)
$P\text{E}'_{O_2}$ (kPa)				
Control	13.79 (0.46)	6.32 (0.35)	6.51 (0.33)	12.52 (0.51)
Placebo	14.01 (0.41)	6.30 (0.42)	6.44 (0.38)	12.28 (0.73)
$S\text{p}_{O_2}$ (%)				
Control	95.4 (1.3)	79.1 (0.7)	79.7 (1.1)	94.9 (1.0)
Placebo	96.1 (1.6)*	79.8 (0.7)*	80.1 (1.4)	95.3 (0.9)
Studied variables				
$\dot{V}\text{E}^{\text{inst}}$ (litre min^{-1})				
Control	8.75	16.21	11.42	8.76
	(7.57, 9.93)	(12.85, 19.57)	(9.24, 13.59)	(7.66, 9.86)
Placebo	9.05	17.78	10.97	8.54
	(7.93, 10.17)	(14.83, 20.73)	(9.20, 12.73)	(7.75, 9.33)
$V\text{T}$ (litre)				
Control	0.565	0.997	0.751	0.632
	(0.50, 0.630)	(0.791, 1.203)	(0.640, 0.861)	(0.578, 0.686)
Placebo	0.578	1.024	0.727	0.573*
	(0.522, 0.633)	(0.849, 1.200)	(0.634, 0.820)	(0.546, 0.601)
f (b.p.m.)				
Control	15.57	16.64	15.45	14.13
	(14.40, 16.75)	(15.07, 18.20)	(14.28, 16.63)	(12.75, 15.52)
Placebo	15.91	17.69*	15.32	15.07
	(14.20, 17.62)	(16.12, 19.26)	(14.12, 16.53)	(13.60, 16.54)
$V\text{T} : T\text{I}$ (litre s^{-1})				
Control	22.88	41.54	31.21	25.15
	(19.89, 25.88)	(32.62, 50.47)	(25.00, 37.43)	(22.38, 27.93)
Placebo	24.06	45.74	30.46	24.13
	(21.00, 27.12)	(37.59, 53.88)	(25.85, 35.07)	(22.29, 25.98)

Table 3 Mean (95 % confidence limits) calculated variables: acute hypoxic response (AHR), hypoxic ventilatory decline (HVD) and the off-response for placebo, clonidine and respective control runs. $^*P < 0.05$ compared with respective control

	AHR (litre min^{-1})	HVD (litre min^{-1})	Off-response (litre min^{-1})
Control	7.46	4.79	2.65
	(4.49, 10.43)	(3.03, 6.55)	(0.40, 4.90)
Placebo	8.73	6.82*	2.43
	(6.34, 11.12)	(5.28, 8.36)	(1.06, 3.80)
Control	10.40	6.49	2.87
	(5.97, 14.83)	(3.92, 9.06)	(0.87, 4.87)
Clonidine	5.81*	3.42*	2.24
	(1.94, 9.68)	(2.35, 4.49)	(−0.83, 5.31)

not allow within-day randomization of clonidine and placebo treatment runs. Because a subject's hypoxic ventilatory response varies from day to day [13], we did not attempt to compare placebo and clonidine treatment runs directly but added in a control hypoxic run which preceded the treatment runs. Both placebo and clonidine treatment runs were compared with their respective controls on the same day. This reduced within-subject variability of hypoxic ventilatory response and the placebo limb of the study allowed an assessment of any fixed order effect on the measured responses.

The ventilatory response to hypoxia requires 1 h to recover completely. If hypoxic tests are performed in succession, the ventilatory response to the second hypoxic test will be attenuated if inadequate time is allowed for complete recovery of the response [14]. In our studies, there was an interval of 1 h between hypoxic runs and we found no reduction in response after placebo treatment. In fact, we found that the hypoxic response after placebo was greater than the preceding control, although this was not statistically significant. It is likely therefore that the hypoxic ventilatory response had recovered completely before our second hypoxic run. Furthermore, the 1-h interval allowed oral clonidine to achieve reasonable plasma concentrations as pharmacokinetic studies have indicated that oral clonidine achieves peak concentrations at 1–2 h [12, 15].

Analysis of variance did not reveal any significant differences in $P\text{E}'_{CO_2}$ in the four measurement periods or in $S\text{p}_{O_2}$ in periods H1 and H2 within runs. However, there were significant changes between treatment and control runs in $S\text{p}_{O_2}$ and $P\text{E}'_{CO_2}$. The

Table 4 Mean (SD) imposed ventilatory variables and mean (95% confidence limits) studied ventilatory variables in the four measurement periods for control and clonidine runs. $^{*}P < 0.05$ compared with control

	Normoxia baseline	Early hypoxia	Late hypoxia	Normoxia recovery
Imposed variables				
$P\mathrm{E}'_{\mathrm{CO_2}}$ (kPa)				
Control	5.10 (0.18)	5.10 (0.15)	5.13 (0.19)	5.10 (0.20)
Clonidine	5.10 (0.20)	5.14 (0.21)	5.22 (0.18)*	5.17 (0.22)
$P\mathrm{E}'_{\mathrm{O_2}}$ (kPa)				
Control	13.45 (0.67)	6.29 (0.44)	6.53 (0.39)	12.64 (0.97)
Clonidine	13.61 (0.55)	6.42 (0.59)	6.69 (0.45)	12.92 (0.69)
$S\mathrm{p}_{\mathrm{O_2}}$ (%)				
Control	95.6 (1.0)	79.9 (0.6)	80.1 (1.0)	94.9 (1.7)
Clonidine	95.0 (1.3)	78.9 (1.0)*	79.8 (1.7)	93.9 (2.1)
Studied variables				
$\dot{V}\mathrm{E}^{\mathrm{inst}}$ (litre min^{-1})				
Control	8.22	18.62	12.14	9.26
	(6.97, 9.47)	(13.37, 23.87)	(9.11, 15.16)	(8.00, 10.52)
Clonidine	8.90	14.71*	11.30	9.06
	(8.19, 9.61)	(11.10, 18.32)	(8.16, 14.44)	(8.43, 9.68)
$V\mathrm{T}$ (litre)				
Control	0.569	1.060	0.753	0.591
	(0.494, 0.644)	(0.839, 1.282)	(0.620, 0.886)	(0.519, 0.662)
Clonidine	0.594	0.878*	0.756	0.591
	(0.557, 0.630)	(0.657, 1.099)	(0.541, 0.971)	(0.555, 0.626)
f (b.p.m.)				
Control	14.86	17.73	16.05	16.33
	(13.52, 16.19)	(14.84, 20.61)	(14.63, 17.47)	(13.99, 18.66)
Clonidine	15.10	17.00	15.15*	15.41
	(13.30, 16.89)	(15.36, 18.63)	(13.83, 16.47)	(14.27, 16.54)
$V\mathrm{T}:T\mathrm{I}$ (litre s^{-1})				
Control	22.26	47.35	33.68	26.94
	(18.71, 25.82)	(34.25, 60.46)	(26.16, 41.21)	(23.27, 30.61)
Clonidine	23.21	37.49*	30.46	23.82
	(21.29, 25.12)	(27.83, 47.14)	(21.60, 39.31)	(22.10, 25.54)

differences in $S\mathrm{p}_{\mathrm{O_2}}$ between runs were very small and well within the error of the pulse oximeter used. Furthermore, $P\mathrm{E}'_{\mathrm{O_2}}$ was not significantly different between runs and as peripheral chemoreceptors respond to a reduction in oxygen tension and not to a decrease in oxygen saturation [16], these small changes in $S\mathrm{p}_{\mathrm{O_2}}$ were of no consequence. Therefore, the hypoxic stimuli were comparable between runs. With $P\mathrm{E}'_{\mathrm{CO_2}}$, the mean differences were less than 0.15 kPa between runs. After placebo, both normoxic baseline and early hypoxia $P\mathrm{E}'_{\mathrm{CO_2}}$ levels were significantly lower than control, but this was not accompanied by a lower $\dot{V}\mathrm{E}^{\mathrm{inst}}$ as expected, suggesting a large behavioural input stimulating breathing. Because $\dot{V}\mathrm{E}^{\mathrm{inst}}$ was not significantly different between placebo and control during these two measurement periods, it is likely that the larger behavioural input after placebo and the lower $P\mathrm{E}'_{\mathrm{CO_2}}$ levels did not affect the results markedly. In contrast, after clonidine, $P\mathrm{E}'_{\mathrm{CO_2}}$ level during late hypoxia was significantly greater than control and this could have overestimated ventilation during late hypoxia, although the effect is likely to have been small.

Two subjects were excluded from analysis because of apparent episodes of obstructive apnoea, mainly during the hypoxic period after clonidine treatment. Neither recalled these obstructive episodes and it is likely that sedation was responsible. Sedation and obstructive apnoeas after oral clonidine have been reported in a previous study [6]. None of the other subjects had clinical evidence of upper airway obstruction after clonidine but it is possible that subclinical obstructive apnoea did occur during the study. However, it is unlikely that our results were caused entirely by the effects of upper airway obstruction. In this study, we were unable to resolve the question of whether or not clonidine reduced the ventilatory response to hypoxia directly or via its sedative effects leading to obstructive apnoeas. It has also been suggested that the ventilatory effects of clonidine may be caused by changes in sleep state [5]. Although our subjects felt sedated after clonidine to varying degrees, none demonstrated a significant reduction in oxygen consumption or carbon dioxide production and neither ventilation nor $P\mathrm{E}'_{\mathrm{CO_2}}$ changed during normoxic baseline after clonidine. Previous work suggests that these variables would be altered if the subjects were asleep [17, 18]. Therefore, our results are unlikely to be caused by a change in sleep state induced by clonidine.

Both AHR and HVD were reduced after clonidine compared with control. This is in keeping with the observation that the magnitude of the hypoxic ventilatory decline is related to the acute hypoxic response [19]. Although the off-response was not significantly different from control, in three of eight subjects, clonidine caused ventilation at the end of hypoxia to be lower than normoxic baseline values. This suggests that in some subjects, under conditions of sustained hypoxia, clonidine may accentuate HVD. However, the number of subjects used in the current study is too small to comment further. An anomaly of this study was that although AHR was not significantly different after placebo compared with control, HVD after placebo was greater (table 3). There is no obvious reason for this. It is possible that this was the result of a placebo effect causing an alteration in behavioural state and ventilatory control.

Human studies have concentrated so far on the influence of clonidine on the hypercapnic ventilatory response. An i.v. dose of 3 $\mu g\ kg^{-1}$ attenuated the hypercapnic response significantly by reducing the slope of the carbon dioxide response line [4]. This was also the case after 300 μg given extradurally [5]. Two studies using oral clonidine (range 3.5–5 $\mu g\ kg^{-1}$) did not demonstrate a reduction in the slope of the carbon dioxide response line [2, 3]. However, Bailey and co-workers did find rightward displacement of the ventilatory response to carbon dioxide after clonidine [2] and Jarvis and co-workers found significant depression of mean inspiratory flow rate ($V_T:T_I$) [3]. Therefore, it is likely that clonidine does alter the ventilatory response to hypercapnia both by reducing the slope and by rightward shift of the response. We chose an oral dose of 3.5 $\mu g\ kg^{-1}$ for our subjects as this was comparable with the doses used in the hypercapnic studies.

Information on the effect of clonidine on the hypoxic ventilatory response in humans is lacking and animal studies have yielded conflicting results. Kou and colleagues [8] demonstrated the presence of α_2 adrenergic receptors in the carotid bodies of cats and that guanabenz, an α_2 agonist similar to clonidine, reduced the carotid sinus nerve discharge in response to hypoxia. In a later study on dogs using dexmedetomidine, a more specific α_2 adrenergic agonist, Nguyen and colleagues [9] found no significant change in the hypoxic ventilatory response. Our study has shown that the initial increase in ventilation in response to hypoxia (lasting 3–8 min) was attenuated by clonidine by an average of 3.91 litre min^{-1} (95% confidence limit 2.27, 5.55 litre min^{-1}) but did not affect the subsequent decline in ventilation when hypoxia was sustained. Animal studies have further suggested that the direct effects of catecholamines, their antagonists and volatile anaesthetic agents on peripheral chemoreceptors disappear in severe hypoxia (< 5.3 kPa) [20, 21]. The effect of clonidine on the hypoxic ventilatory response may be overcome by more severe hypoxia, but as we only examined the effect of clonidine at one level of hypoxia, we cannot predict the effect in more severe hypoxia. The exact mechanism by which clonidine reduced the hypoxic ventilatory response remains unclear. The peripheral chemoreceptors may be involved but a central effect of clonidine cannot be excluded.

This effect of clonidine could have contributed to the episodes of oxygen desaturation reported by previous investigators [6, 7]. However, these investigators suggested that obstructive apnoeas caused by sedation after clonidine were responsible for the instability in oxygenation. Apart from its sedative action, clonidine may exacerbate these obstructive apnoeas via an effect on peripheral chemoreceptors. Increased arousal from chemical stimuli to breathing increases the tone of upper airway muscles, and hypoxia is an important stimulus [22]. Clonidine may have attenuated this reflex at the peripheral chemoreceptors. Therefore, it is likely that clonidine can cause oxygen desaturations through both its sedative effect and via an effect on the peripheral chemoreflex pathway.

In conclusion, we have demonstrated that clonidine reduced the initial increase and subsequent reduction in ventilation during sustained hypoxia. However, the absolute level of ventilation at the end of the hypoxic period was unchanged. Blunting of this protective mechanism suggests that the use of clonidine in patients requires respiratory monitoring, especially when used with other agents which depress ventilation.

Acknowledgement

We thank the Sir Stanley and Lady Davidson bequest of the University of Edinburgh for funds for consumables and Boehringer Ingelheim for clonidine and placebo tablets. I. T. Foo was a *British Journal of Anaesthesia* research fellow.

References

1. Aantaa R, Scheinin M. Alpha$_2$-adrenergic agents in anaesthesia. *Acta Anaesthesiologica Scandinavica* 1993; 37: 433–448.
2. Bailey PL, Sperry RJ, Johnson GK, Eldredge SJ, East KA East TD, Pace NL, Stanley TH. Respiratory effects of clonidine alone and combined with morphine, in humans. *Anesthesiology* 1991; 74: 43–48.
3. Jarvis DA, Duncan SR, Segal IS, Maze M. Ventilatory effects of clonidine alone and in the presence of alfentanil, in human volunteers. *Anesthesiology* 1992; 76: 899–905.
4. Ooi R, Pattison J, Feldman SA. The effects of intravenous clonidine on ventilation. *Anaesthesia* 1991; 46: 632–633.
5. Penon C, Ecoffey C, Cohen SE. Ventilatory response to carbon dioxide after epidural clonidine injection. *Anesthesia and Analgesia* 1991; 72: 761–764.
6. Benhamou D, Veillette Y, Narchi P, Ecoffey C. Ventilatory effects of premedication with clonidine. *Anesthesia and Analgesia* 1991; 73: 799–803.
7. Narchi P, Benhamou D, Hamza J, Bouaziz H. Ventilatory effects of epidural clonidine during the first 3 hours after caesarean section. *Acta Anaesthesiologica Scandinavica* 1992; 36: 791–795.
8. Kou YR, Ernsberger P, Cragg PA, Cherniack NS, Prabhakar NR. Role of α_2-adrenergic receptors in the carotid body response to isocapnic hypoxia. *Respiration Physiology* 1991; 83: 353–364.
9. Nguyen D, Abdul-Rasool I, Ward D, Hsieh J, Kobayashi D, Hadlock S, Singer F, Bloor B. Ventilatory effects of dexmedetomidine, atipamezole, and isoflurane in dogs. *Anesthesiology* 1992; 76: 573–579.
10. Young CH, Drummond GB, Warren PM. Effect of a subanaesthetic concentration of halothane on the ventilatory response to sustained hypoxia in healthy humans. *British Journal of Anaesthesia* 1993; 71: 642–647.
11. White DP, Douglas NJ, Pickett CK, Weil JV, Zwillich CW. Sexual influence on the control of breathing. *Journal of Applied Physiology* 1983; 54: 874–879.
12. Arndts D, Doevendans J, Kirsten R, Heintz B. New aspects of the pharmacokinetics and pharmacodynamics of clonidine in man. *European Journal of Clinical Pharmacology* 1983; 24: 21–30.
13. Sahn SA, Zwillich CW, Dick N, McCullough RE, Lakshminarayan S, Weil JV. Variability of ventilatory responses to hypoxia and hypercapnia. *Journal of Applied Physiology* 1977; 43: 1019–1025.
14. Easton PA, Slykerman LJ, Anthonisen NR. Recovery of the ventilatory response to hypoxia in normal adults. *Journal of Applied Physiology* 1988; 64: 521–528.
15. Dollery CT, Davies DS, Draffan GH, Dargie HJ, Dean CR,

Reid JL, Clare RA, Murray S. Clinical pharmacology and pharmacokinetics of clonidine. *Clinical Pharmacology and Therapeutics* 1976; **19**: 11–17.

16. Comroe JH, Schmidt CF. The part played by reflexes from the carotid body in the chemical regulation of respiration in the dog. *American Journal of Physiology* 1938; **121**: 75–97.
17. White DP, Weil JV, Zwillich CW. Metabolic rate and breathing during sleep. *Journal of Applied Physiology* 1985: **59**: 384–391.
18. Douglas NJ, White DP, Pickett CK, Weil JV, Zwillich CW. Respiration during sleep in normal man. *Thorax* 1982; **37**: 840–844.
19. Easton PA, Slykerman LJ, Anthonisen NR. Ventilatory response to sustained hypoxia in normal adults. *Journal of Applied Physiology* 1986; **61**: 906–911.
20. Ponte J, Sadler CL. Interactions between hypoxia, acetylcholine and dopamine in the carotid body of rabbit and cat. *Journal of Physiology (London)* 1989; **410**: 395–410.
21. Ponte J, Sadler CL. Effect of halothane, enflurane and isoflurane on carotid body chemoreceptor activity in the rabbit and cat. *British Journal of Anaesthesia* 1989; **62**: 33–40.
22. Parisi RA, Santiago TV, Edelman NH. Genioglossal and diaphragmatic EMG responses to hypoxia during sleep. *American Review of Respiratory Disease* 1988; **138**: 610–616.

British Journal of Anaesthesia 1996; **76**: 221–226

Comparison of nicardipine, diltiazem and verapamil for controlling the cardiovascular responses to tracheal intubation

K. MIKAWA, K. NISHINA, N. MAEKAWA AND H. OBARA

Summary

We have compared the efficacy of three calcium channel blockers, nicardipine, diltiazem and verapamil, in attenuating the cardiovascular responses to laryngoscopy and intubation in 60 normotensive patients (ASA I) undergoing rapid sequence induction of anaesthesia with thiopentone and fentanyl. We also examined whether or not these blockers inhibited catecholamine release induced by intubation. The patients were allocated to one of four groups ($n = 15$ for each): saline (control), nicardipine 30 µg kg^{-1}, diltiazem 0.2 mg kg^{-1} or verapamil 0.1 mg kg^{-1}. Verapamil and the three other drugs were administered 45 s and 60 s before the start of direct laryngoscopy, respectively, in a double-dummy design. Anaesthesia was induced with thiopentone 4 mg kg^{-1} i.v. and fentanyl 2 µg kg^{-1} i.v. Tracheal intubation was facilitated with vecuronium 0.2 mg kg^{-1}. During anaesthesia, ventilation was assisted or controlled with 1% isoflurane and 50% nitrous oxide in oxygen. Laryngoscopy lasting 30 s was attempted 2 min after administration of thiopentone and vecuronium. Patients receiving saline exhibited significant increases in systolic and diastolic arterial pressures (AP), heart rate (HR) and plasma concentrations of catecholamines associated with tracheal intubation. The increase in AP was attenuated in patients treated with any calcium channel blocker. The greatest effect was elicited by verapamil, which attenuated the increase in HR, although nicardipine seemed to enhance tachycardia. All three drugs failed to suppress the increase in plasma catecholamine concentrations in response to tracheal intubation. These findings suggest that bolus injection of verapamil 0.1 mg kg^{-1} was a more effective method of controlling hypertension and tachycardia associated with intubation than diltiazem 0.2 mg kg^{-1} or nicardipine 30 µg kg^{-1}, and that these prophylactic effects were not caused by inhibition of the catecholamine response. (*Br. J. Anaesth.* 1996; **76**: 221–226)

Key words

Intubation tracheal responses. Calcium channel block, diltiazem. Calcium channel block, nicardipine. Calcium channel block, verapamil. Complications, hypertension. Cardiovascular system, effects.

Laryngoscopy and tracheal intubation after a standardized induction dose of thiopentone often provoke a reflex increase in both sympathetic and sympathoadrenal activity, which may result in hypertension, tachycardia and arrhythmias [1–7]. These responses, although transient, may be harmful in some patients, particularly those suffering from myocardial or cerebrovascular disease. Many pharmacological techniques have been devised to reduce the extent of the haemodynamic events, including the use of high-dose opioids [1], local anaesthetics [1], adrenergic blocking agents [1] and vasodilating agents such as nitroglycerin [2] and sodium nitroprusside [3]. Several studies have shown that calcium channel blockers such as nicardipine [4], diltiazem [5] or verapamil [6, 7] are also effective. However, the effects of these calcium channel blockers have been examined separately with different anaesthetic induction techniques, including different anaesthetics and neuromuscular blockers. Thus the aim of the present study was to compare the efficacy of single rapid administration of verapamil, diltiazem and nicardipine for controlling these haemodynamic responses to tracheal intubation under the same anaesthetic techniques.

A good correlation has been demonstrated between the cardiovascular responses to intubation and changes in plasma catecholamine concentrations [8–11]. Calcium ions exert a major role in the release of catecholamines from the adrenal gland and adrenergic nerve endings, which affects plasma concentrations of catecholamines, in response to sympathetic stimulation [12]. Animal experiments have shown that calcium channel blockers inhibited catecholamine release from the sympathetic nerve ending by electrical stimulation [13–15]. In a study in healthy volunteers, the blocker inhibited the increase in plasma adrenaline induced by exercise [16]. These observations suggest that calcium channel blockers interfere with catecholamine release after tracheal intubation. In addition, therefore, plasma concentrations of catecholamines were measured before and after intubation with or without prior administration of the calcium channel blockers.

Patients and methods

The study was approved by the Ethics Committee of Kobe University Hospital. We studied 60 normo-

---

KATSUYA MIKAWA, MD, KAHORU NISHINA, MD, NOBUHIRO MAEKAWA, MD, HIDEFUMI OBARA, MD, Department of Anaesthesiology, Kobe University School of Medicine, Kusunoki-cho 7, Chuo-ku, Kobe, 650, Japan. Accepted for publication: September 5, 1995.

Correspondence to K.M.

Table 1 Patient characteristics (mean (SD) [range] or number). No significant differences between groups

	Saline (control)	Nicardipine 30 μg kg^{-1}	Diltiazem 0.2 mg kg^{-1}	Verapamil 0.1 mg kg^{-1}
Patients (*n*)	15	15	15	15
Sex (M/F)	4/11	6/9	8/7	7/8
Age (yr)	44 [21–68]	47 [26–67]	43 [21–64]	44 [25–65]
Weight (kg)	54 (9) [42–69]	55 (11) [40–71]	57 (10) [43–75]	55 (10) [45–72]
Height (cm)	159 (7) [148–176]	160 (8) [151–178]	162 (9) [149–180]	160 (9) [149–177]

tensive patients (ASA I) undergoing elective surgery; all gave informed consent. They were allocated randomly to one of four groups ($n = 15$ for each group) to receive saline (control), nicardipine 30 μg kg^{-1} (Perdipine, Yamanouchi, Japan), diltiazem 0.2 mg kg^{-1} (Herbesser, Tanabe, Japan) or verapamil 0.1 mg kg^{-1} (Vasolan, Eisai, Japan). Patients with anticipated difficult tracheal intubation, hypertension, renal, hepatic or gastrointestinal disease, or weight exceeding 120% of ideal for height were excluded (Table 1).

Premedication consisted of oral diazepam 0.1 mg kg^{-1} and atropine 0.01 mg kg^{-1} i.m., given at 60 min and 30 min, respectively, before induction of anaesthesia, which started at 08:30 in all subjects. On arrival in the operating room, two (right and left) radial arterial cannulae were inserted under local anaesthesia for continuous monitoring of systolic (SAP) and diastolic (DAP) arterial pressure using a Cardiocap (Datex, Helsinki, Finland) and for blood sampling for measurement of plasma concentrations of catecholamines. Heart rate (HR) was monitored by electrocardiography (ECG lead II). After a 10-min stabilization period, the patients breathed 100% oxygen via a mask for 3 min. Immediately before induction of anaesthesia (time = 0), arterial blood was obtained for catecholamine analysis, and SAP, DAP and HR were recorded simultaneously by independent observers to obtain the operating room baseline. Anaesthesia was then induced in a rapid sequence fashion with thiopentone 4 mg kg^{-1} and fentanyl 2 μg kg^{-1} followed by vecuronium 0.2 mg kg^{-1} to facilitate tracheal intubation. Direct laryngoscopy was attempted 2 min after thiopentone–vecuronium and maintained for 30 s. The tracheal tube was inserted within the last 5 s of laryngoscopy with the aid of a standard Macintosh laryngoscope blade. All intubations were performed by the same anaesthetist (K.M.). A double–dummy technique was used to maintain a double-blind design (table 2). All patients received two injections. In the verapamil group, saline and verapamil were administered i.v. 60 s and 45 s before the start of direct laryngoscopy, respectively. In the diltiazem and nicardipine groups, the calcium channel blocker and saline were injected 60 s and 45 s before starting laryngoscopy. These doses and timings were based on our previous data [4–6]. In these reports, the three calcium channel blockers were shown to attenuate the pressor response to tracheal intubation to a similar extent (16–18% attenuation of mean arterial pressure). Furthermore, the doses of the calcium channel blockers used in the present study produced a similar degree of hypotension in patients anaesthetized with enflurane and nitrous oxide, without noxious surgical stimulation [4–6]: nicardipine 30 μg kg^{-1}, verapamil 0.1 mg kg^{-1} and diltiazem 0.2 mg kg^{-1} decreased mean arterial pressure by 30%, 27% and 24%, respectively. Other investigators administered nicardipine and diltiazem for the treatment of hypertension during surgery [17, 18]. Nicardipine 25–30 μg kg^{-1} produced a 25% reduction in SAP [17] while diltiazem 10 mg (0.2 mg kg^{-1} by estimation) i.v. decreased SAP by 21% [18]. Verapamil 0.1 mg kg^{-1} or 5 mg i.v. caused a 25% decrease in SAP in patients with renal hypertension [19]. These findings determined our selection of the doses of the three calcium channel blockers.

After administration of thiopentone and vecuronium until 10 min after induction, ventilation was assisted as required or controlled with 1% isoflurane and 50% nitrous oxide in oxygen, and end-tidal partial pressure of carbon dioxide was maintained at 4.1–5.1 kPa, monitored with a Datex Capnometer (Helsinki, Finland) by means of a catheter placed in the nostril. After insertion of the tracheal tube, sampling of expired air was performed from a T-piece connected to the tube. Additional blood samples and haemodynamic measurements were obtained immediately before induction, and 1, 2, 2.5, 2.75, 3, 4 and 5 min after administration of thiopentone–vecuronium by independent observers who were blinded to the nature of the experimental treatment. All measurements and blood sampling were completed before surgical skin incision. SAP, DAP, HR and plasma concentrations of catecholamines were compared with corresponding measurements in the four groups and with measurements

Table 2 Timing of administration of calcium channel blockers and saline in the four groups (double-dummy technique). All doses of drug were prepared in 10 ml

	First drug	Second drug
Group	60 s after thiopentone–vecuronium (60 s before laryngoscopy)	75 s after thiopentone–vecuronium (45 s before laryngoscopy)
Control	Saline	Saline
Nicardipine	Nicardipine 30 μg kg^{-1}	Saline
Diltiazem	Diltiazem 0.2 mg kg^{-1}	Saline
Verapamil	Saline	Verapamil 0.1 mg kg^{-1}

before induction (operating room baseline) within the same group. Maximal values of SAP, DAP and HR after intubation were also recorded.

CATECHOLAMINE MEASUREMENT

Arterial blood for measurement of plasma concentrations of catecholamine, was collected in lithium heparin tubes and centrifuged within 10 min at 0 °C. Plasma was separated and stored at −70 °C until assay by reverse phase high-pressure liquid chromatography with electrochemical detection and an internal standard using the method described by Krstulovic [20] and Causon and Carruthers [21]. The lower limits of sensitivity of the method were 54.6 pmol litre^{-1} and 0.0591 nmol litre^{-1} for adrenaline and noradrenaline, respectively. The intra- and inter-assay coefficients of variance were, respectively, 4.4 % and 8.0 % for adrenaline and 4.8 % and 8.4 % for noradrenaline.

STATISTICS

Statistical analysis was performed using analysis of variance followed by Bonferroni's modification of *t* test for parametric data, and Fisher's exact test for non-parametric (distribution) data. Differences were considered statistically significant at $P < 0.05$. The power of the present study was 75 % provided that d $(= \mu - \mu'/\sigma)$ is 1.0 (where μ, μ' = mean and σ = SD). Thus the number of patients in the present study ($n = 15$) was sufficient to detect such a difference between groups.

Results

The four groups were comparable in age, weight and sex (table 1).

There were no significant differences between the four groups in SAP immediately before the start of laryngoscopy or before induction. In response to laryngoscopy and intubation, SAP and DAP increased significantly in the control group, while the increases were significantly less in the groups treated with calcium channel blockers (figs 1, 2). Administration of verapamil 0.1 mg kg^{-1} completely inhibited the increase in arterial pressures associated with intubation. Diltiazem 0.2 mg kg^{-1} seemed to be less effective than the two other calcium channel blockers. Conversely, in the verapamil group, arterial pressures decreased 5 min after induction compared with before induction, although the two other blockers did not cause such hypotension.

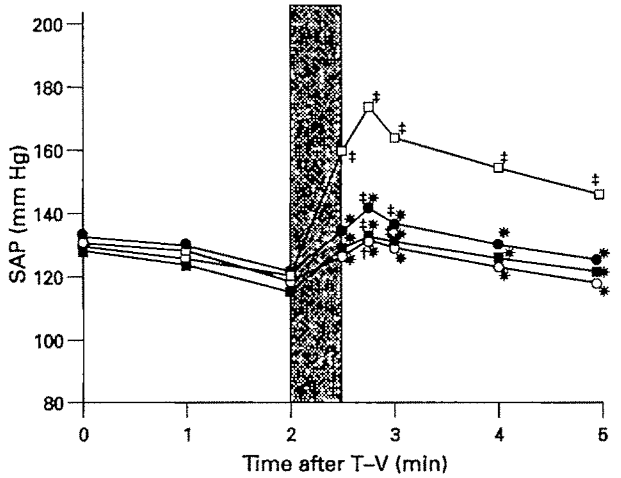


Figure 1 Mean changes in systolic arterial pressure (SAP) after thiopentone–vecuronium (T–V) and in response to laryngoscopy and tracheal intubation with prior calcium channel blockers or saline (□) (control). Nicardipine 30 μg kg^{-1} (■), diltiazem 0.2 mg kg^{-1} (●) and verapamil 0.1 mg kg^{-1} (○) were administered i.v. 60 s, 60 s and 45 s before the start of laryngoscopy, respectively. SEM bars are omitted for clarity. The shaded area = duration of laryngoscopy and tracheal intubation. $^{*}P < 0.05$ *vs* control; $\dagger P < 0.05$ *vs* diltiazem; $\ddagger P < 0.05$ *vs* pre-induction values within groups.

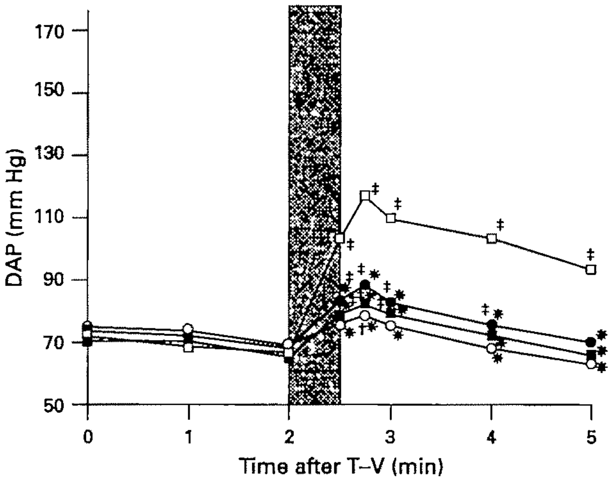


Figure 2 Mean changes in diastolic arterial pressure (DAP) after thiopentone–vecuronium (T–V) and in response to laryngoscopy and tracheal intubation with prior calcium channel blockers (nicardipine 30 μg kg^{-1} (■), diltiazem 0.2 mg kg^{-1} (●) and verapamil 0.1 mg kg^{-1} (○) or saline (□) (control). SEM bars are omitted for clarity. The shaded area = duration of laryngoscopy and tracheal intubation. $^{*}P < 0.05$ *vs* control; $\dagger P < 0.05$ *vs* diltiazem; $\ddagger P < 0.05$ *vs* pre-induction values within groups.

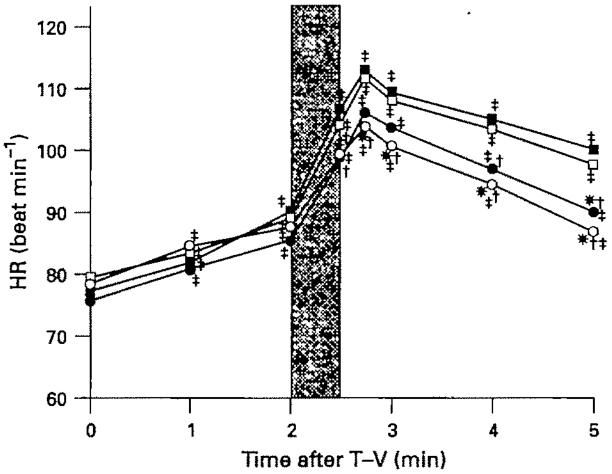


Figure 3 Mean changes in heart rate (HR) after thiopentone–vecuronium (T–V) and in response to laryngoscopy and tracheal intubation with prior calcium channel blockers (nicardipine 30 μg kg^{-1} (■), diltiazem 0.2 mg kg^{-1} (●) and verapamil 0.1 mg kg^{-1} (○)) or saline (□) (control). SEM bars are omitted for clarity. The shaded area = duration of laryngoscopy and tracheal intubation. $^{*}P < 0.05$ *vs* control; $\dagger P < 0.05$ *vs* nicardipine; $\ddagger P < 0.05$ *vs* pre-induction values within groups.

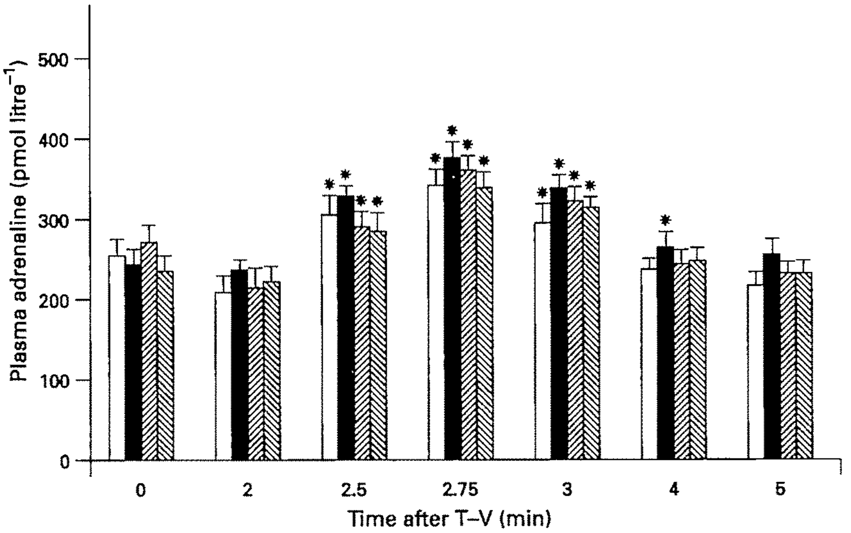


Figure 4 Changes in plasma adrenaline concentrations (mean, SEM) after thiopentone–vecuronium (T–V) and in response to laryngoscopy and tracheal intubation with prior calcium channel blockers (nicardipine 30 µg kg^{-1} (■), diltiazem 0.2 mg kg^{-1} (▨) and verapamil 0.1 mg kg^{-1} (▧)) or saline (□) (control). Data at 1 min after induction are omitted. *$P < 0.05$ *vs* pre-induction values within groups.

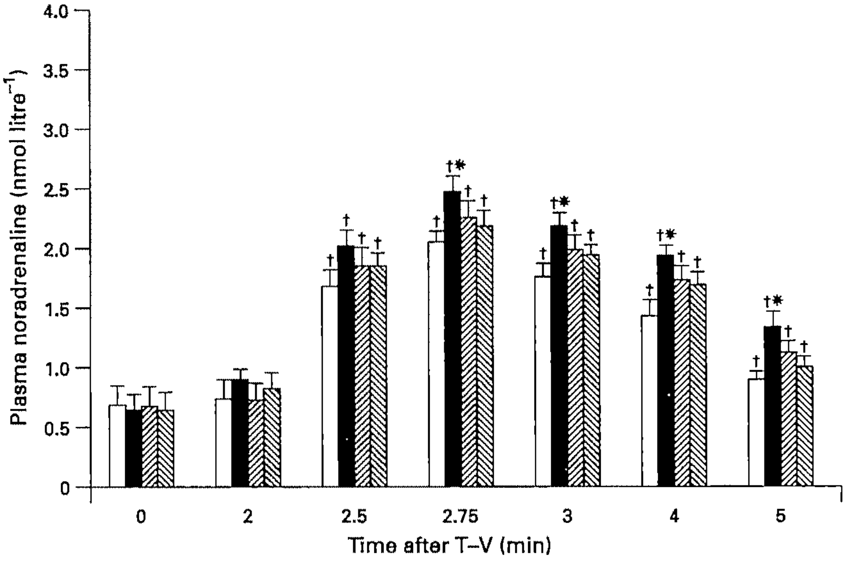


Figure 5 Changes in plasma noradrenaline concentrations (mean, SEM) after thiopentone–vecuronium (T–V) and in response to laryngoscopy and tracheal intubation with prior calcium channel blockers (nicardipine 30 µg kg^{-1} (■), diltiazem 0.2 mg kg^{-1} (▨) and verapamil 0.1 mg kg^{-1} (▧)) or saline (□) (control). Data at 1 min after induction are omitted. *$P < 0.05$ *vs* control; †$P < 0.05$ *vs* pre-induction values within groups.

Although there was an increase in HR after induction, there was no significant difference in pre-induction values of HR or that immediately before laryngoscopy between the four groups. Verapamil successfully attenuated the HR increase after intubation (fig. 3). In contrast, nicardipine failed to do so. HR was lower in the verapamil and diltiazem groups than in the nicardipine group.

There were no significant differences in plasma adrenaline and noradrenaline concentrations between the four groups at the pre-induction and pre-intubation times. Plasma adrenaline concentrations increased significantly after intubation, with return towards baseline by 5 min after induction in all groups (fig. 4). The calcium channel blockers failed to attenuate the increase. Plasma noradrenaline concentrations increased in response to intubation in the control group. The increase was enhanced in patients receiving nicardipine (fig. 5). Verapamil and diltiazem showed changes similar to those in the control group.

A significantly smaller number of patients receiving calcium channel blockers demonstrated an SAP > 170 mm Hg and a DAP > 110 mm Hg (table 3). The number of patients with HR > 100 beat min^{-1} seemed to be smaller in the verapamil than in the control group, although this was not significant. HR > 100 beat min^{-1} was observed less frequently in patients receiving verapamil than in those receiving nicardipine.

No abnormal changes in ECG were observed in any patient in the diltiazem and verapamil groups. In contrast, one patient in the control and nicardipine groups had short-lived ventricular premature con-

Table 3 Number of patients demonstrating systolic (SAP) or diastolic (DAP) hypertension and tachycardia by treatment groups ($n = 15$ for each group). Significant difference ($P < 0.05$) compared with: * control group, † nicardipine group

	SAP > 170 mm Hg	DAP > 110 mm Hg	Heart rate > 100 beat min^{-1}
Saline (control)	8	9	13
Nicardipine 30 μg kg^{-1}	0*	0*	14
Diltiazem 0.2 mg kg^{-1}	2*	1*	11
Verapamil 0.1 mg kg^{-1}	0*	0*	9†

tractions. During this study, no patient developed hypotension ($SAP < 80$ mm Hg) or bradycardia ($HR < 50$ beat min^{-1}) severe enough to require pressor, anticholinergic or sympathomimetic agents: the lowest SAP/DAP values were 82/49, 82/50 and 85/52 mm Hg in the verapamil, nicardipine and diltiazem groups, respectively, and the lowest HR were 57, 79 and 63 beat min^{-1} in the verapamil, nicardipine and diltiazem groups, respectively.

Discussion

Consistent with previous reports [4–7], we have confirmed that these calcium channel blockers attenuated hypertension associated with tracheal intubation. Verapamil successfully blunted tachycardia, unlike nicardipine and diltiazem. These findings may be explained by the difference in pharmacological characteristics between dihydropyridines and phenylalkylamines. In our previous study [6], verapamil failed to attenuate the increase in HR. This discrepancy may result from different anaesthetic induction techniques: we administered fentanyl as a supplement in the present study. The concomitant use of fentanyl has been shown to potentiate the slowing effect of verapamil on HR [22]. Although we reported previously that diltiazem 0.3 mg kg^{-1} was more effective against the pressor response than 0.2 mg, our preliminary study revealed that the dose of 0.3 mg in the present study caused severe hypotension ($SAP < 75$ mm Hg) in two of five patients. This may result from interaction between diltiazem and fentanyl. Thus these observations did not justify the use of this dose.

In patients with coronary artery disease (CAD) or those with risk factors for CAD, myocardial ischaemia may occur during the induction–intubation sequence [23]. Intraoperative ischaemia has been associated with a high rate of perioperative myocardial infarction. Because HR is a major determinant of myocardial oxygen balance [24], the effect of verapamil on tachycardia may justify the use of the drug, whereas the lack of efficacy of nicardipine may limit its usefulness.

We have also confirmed previous findings [8–11] that laryngoscopy and tracheal intubation after a combination of thiopentone and a neuromuscular blocking agent cause significant increases in plasma concentrations of catecholamines. No calcium channel blocker attenuated the catecholamine response to intubation, and conversely nicardipine enhanced the increase. Some investigators have documented that short-term treatment using dihydropyridine-type drugs increases plasma concentrations of noradrenaline as a result of baroceptor-mediated reflex in sympathetic nervous activity [25, 26]. Furthermore, verapamil and diltiazem had no effect on plasma concentrations of noradrenaline [27, 28]. These reports support our observations. In the present study, despite higher plasma concentrations of noradrenaline in patients receiving nicardipine than in the control after intubation, the increase in arterial pressure was lower in the nicardipine group during the study period. Philipp, Distler and Cordes documented that an important determinant of the level of arterial pressure may be plasma noradrenaline and reactivity to noradrenaline [29]. Calcium channel blockers have been shown to reduce the pressor effect of circulating noradrenaline on resistance vessels [30], resulting from inhibition of the calcium influx that accompanies stimulation of α_2 receptors [31], leading to attenuation of the increase in arterial pressure after elevated concentrations of noradrenaline.

No patient in the present study developed severe hypotension: the lowest SAP and DAP recorded were 82 mm Hg and 49 mm Hg, respectively, in a patient receiving verapamil 5 min after induction. There were no differences between the three groups in clinical outcome (e.g. intra- and postoperative mortality and morbidity), possibly because we studied only otherwise healthy ASA I patients without cardiovascular or cerebrovascular disease.

References

1. Ng WS. Pathophysiological effects of tracheal intubation. In: Latto IP, Rosen M, eds. *Difficulties in Tracheal Intubation.* Eastbourne: Baillière Tindall, 1985; 12–35.
2. Fassoulaki A, Kaniaris P. Intranasal administration of nitroglycerin attenuates the pressor response to laryngoscopy and intubation of the trachea. *British Journal of Anaesthesia* 1983; **55**: 49–52.
3. Stoelting RK. Attenuation of blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside. *Anesthesia and Analgesia* 1979; **58**: 116–119.
4. Mikawa K, Obara H, Kusunoki M. The effect of nicardipine on the cardiovascular response to tracheal intubation. *British Journal of Anaesthesia* 1990; **64**: 240–242.
5. Mikawa K, Ikegaki J, Maekawa N, Goto R, Kaetsu H, Obara H. The effect of diltiazem on the cardiovascular response to tracheal intubation. *Anaesthesia* 1990; **45**: 289–293.
6. Yaku H, Mikawa K, Maekawa N, Obara H. Effect of verapamil on the cardiovascular responses to tracheal intubation. *British Journal of Anaesthesia* 1992; **68**: 85–89.
7. Puri GD, Singh SP, Singh H, Batra YK. Attenuation of pulse rate and blood pressure response to laryngoscopy and intubation with verapamil. *Indian Journal of Medical Research* 1986; **84**: 548–551.
8. Russel WJ, Morris RG, Frewin DB, Drew SE. Changes in plasma catecholamine concentration during endotracheal intubation. *British Journal of Anaesthesia* 1981; **53**: 837–839.

9. Derbyshire DR, Chmielewski A, Fell D, Vater M, Achola KJ, Smith G. Plasma catecholamine responses to tracheal intubation. *British Journal of Anaesthesia* 1983; **55**: 855–860.
10. Shribman AJ, Smith G, Achola KJ. Cardiovascular and catecholamine responses to laryngoscopy with and without tracheal intubation. *British Journal of Anaesthesia* 1987; **59**: 295–299.
11. Derbyshire DR, Smith G. Sympathoadrenal responses to anaesthesia and surgery. *British Journal of Anaesthesia* 1984; **56**: 725–739.
12. Rasmussen H. The calcium messenger system. *New England Journal of Medicine* 1986; **314**: 1164–1170.
13. Pinto JEB, Trifaro JM. The different effects of D-600 (methoxyverapamil) on the release of adrenal catecholamines induced by acetylcholine, high potassium, or sodium deprivation. *British Journal of Pharmacology* 1976; **57**: 127–132.
14. Cohen J, Gutman Y. Effects of verapamil, dantrolene and lanthanum on catecholamine release from rat adrenal medula. *British Journal of Pharmacology* 1979; **65**: 641–645.
15. Tsuda K, Hano T, Ueshima K, Kuchii M, Nishio I, Masuyama Y. Effects of Ca-antagonists on noradrenaline release from sympathetic nerve endings. *Japanese Pharmacology and Therapeutics* 1983; **11**: 315–316.
16. Defer G, Guezennec YC, Lhoste F. Effect of nifedipine on plasma catecholamines in man at rest and during exercise. *European Journal of Clinical Pharmacology* 1986; **30**: 727–729.
17. Kumura E, Tanaka S, Takaori M. The use of nicardipine during anesthesia and its hypotensive effect (authors' translation). *Rinsho Masui* 1984; **8**: 981–985.
18. Takata M, Nakagawa T, Kiyota T, Nakamura F, Miyano H. The effect of diltiazem hydrochloride on intraoperative hypertension (authors' translation). *Rinsho Masui* 1986; **10**: 299–304.
19. Frishman WH, Peled HB, Kimmel B, Charlap S, Beer N. Calcium entry blockers for the treatment of severe hypertension and hypertensive crisis. *American Journal of Medicine* 1984; 77(2B): 35–45.
20. Krstulovic AM. Investigations of catecholamine metabolism using high-performance liquid chromatography. *Journal of Chromatography* 1982; **229**: 1–34.
21. Causon RC, Carruthers ME. Measurement of catecholamines in biological fluids by high-performance liquid chromatography. *Journal of Chromatography* 1982; **229**: 301–309.
22. Yokota S, Takigawa C, Nakamura I, Kaseno S, Kemmotsu O. Effects of fentanyl and verapamil on atrioventricular conduction in dogs. *Circulatory Control* 1987; **8**: 529–535.
23. Estafanous FE, Tarazi RC. Systemic arterial hypertension associated with cardiac surgery. *American Journal of Cardiology* 1980; **46**: 684–694.
24. Sill JC. Prevention and treatment of myocardial ischemia and dysfunction. In: Tarhan S, ed. *Anesthesia and Coronary Artery Surgery*. Chicago: Year Book Medical Publishers, 1986; 218–268.
25. Pedrinelli R, Fouad FM, Tarazi RC, Bravo EL, Textor SC. *Archives of Internal Medicine* 1986; **146**: 62.
26. Bellet M, Sassano P, Guyenne T, Corvol P, Menard J. Converting-enzyme inhibition buffers the counter-regulatory response to acute administration of nicardipine. *British Journal of Clinical Pharmacology* 1987; **24**: 465–472.
27. Leonetti G, Cuspidi C, Sampieri L, Terzoli L, Zanchetti A. Comparison of cardiovascular, renal, and humoral effects of acute administration of two calcium channel blockers in normotensive and hypertensive subjects. *Journal of Cardiovascular Pharmacology* 1982; **4**: S319–S324.
28. Evans RR, Davis WR, Wallace JM, DiPette DJ, Holland OB. Humoral factors determining the blood pressure response to converting enzyme inhibition and calcium channel blockade. *American Journal of Hypertension* 1990; **3**: 605–610.
29. Philipp Th, Distler A, Cordes U. Sympathetic nervous system and blood pressure control in essential hypertension. *Lancet* 1978; **II**: 959–963.
30. Magometschnigg D, Hötnagl, Rameis H. Diltiazem and verapamil: functional antagonism of exogenous noradrenaline and angiotensin II in man. *European Journal of Clinical Pharmacology* 1984; **26**: 303–307.
31. Van Zwieten PA, Van Meel JCA, Timmermans PBMWM. Calcium antagonists and α_2 adrenoceptors: possible role of extracellular calcium ions in α_2 adrenoceptor-mediated vasoconstriction. *Journal of Cardiovascular Pharmacology* 1982; **4**: S273–S279.

British Journal of Anaesthesia 1996; **96**: 227–234

Preoperative infusion of amino acids prevents postoperative hypothermia

E. SELLDÉN, R. BRÄNSTRÖM AND T. BRUNDIN

Summary

Intraoperative infusion of amino acids has been found to stimulate energy expenditure and thereby prevent anaesthesia-induced hypothermia. Rectal temperature and respiratory gas exchange were measured in 24 female patients before and after isoflurane anaesthesia. Sixteen patients had an amino acid mixture of 240 kJ h^{-1}, infused over 1–2 h before anaesthesia and eight control patients received saline. We compared the results with data from six female volunteers treated with amino acids; they were not premedicated or anaesthetized. In lorazepam premedicated patients, amino acids increased the pre-anaesthesia temperature by 0.3 °C h^{-1}, twice that observed in the volunteers. At awakening after anaesthesia, energy expenditure increased to 50–60% above baseline in the amino acid treated patients, while in the control patients, receiving saline, no increase occurred, despite vigorous shivering. Amino acid infusion prevented hypothermia by increasing heat accumulation and causing delayed stimulation of heat production. The heat accumulation response to amino acid infusion was increased after premedication with lorazepam. (*Br. J. Anaesth.* 1996; **76**: 227–234)

Key words
Hypothermia. Protein, amino acids. Temperature, body. Temperature, metabolism.

Anaesthesia-induced hypothermia constitutes a clinical problem by causing impaired blood coagulation [1], prolonged drug action [2], negative postoperative nitrogen balance [3] and reduced resistance to surgical wound infections [4]. Consequently, several devices to combat hypothermia have been developed [5, 6]. Most of these are designed to minimize heat loss from the body surface. However, general anaesthesia does not induce hypothermia solely by interfering with regulation of heat dissipation. Most anaesthetics also reduce considerably heat generation by suppressing whole body oxidative metabolism [7–9]. Little attention has been paid to preventing the development of anaesthesia-induced hypothermia by stimulating the generation of heat.

It is well known from earlier studies that in the unanaesthetized state, administration of nutrients, especially protein and amino acid mixtures, stimulates resting energy expenditure (see [10]). Moreover, approximately 60 % of the extra heat produced in response to amino acid administration accumulates, thus increasing the temperature of mixed venous blood [11–14]. We recently found that the mechanisms for nutrient-induced thermogenesis are not impaired during general anaesthesia [15]. In contrast, the thermic effect of amino acids was found to be increased five-fold during, and most markedly, immediately after isoflurane–nitrous oxide anaesthesia. The enhanced amino acid-induced thermogenesis counteracted the anaesthesia-induced reduction in metabolism and prevented the development of hypothermia. However, amino acid infusions started at the onset of anaesthesia did not prevent the initial reduction in temperature that occurred within the first 20 min of anaesthesia [15].

The present study was designed to see if starting or completing the amino acid infusion before the onset of anaesthesia would induce heat production, which would be more effective in reducing the initial decrease in temperature and thereby counteract the development of anaesthesia-induced hypothermia more effectively than intraoperative infusions. Therefore, patients admitted for elective surgery were given amino acid infusions over 1–2 h before induction of anaesthesia. Body temperature was measured before, during and after anaesthesia. Energy expenditure was measured before amino acid infusions, immediately before and soon after anaesthesia. The results were compared with those from a control patient group receiving nutrient-free saline solutions, and a group of healthy individuals not subjected to premedication or anaesthesia.

Patients and methods

We studied 24 female patients and six healthy women. The patients were undergoing hysterectomy because of menorrhagia and were otherwise healthy, receiving no medications (table 1). Eight of the patients (group A) had amino acids infused i.v. for 1 h before anaesthesia and continuing throughout the first hour of anaesthesia. Eight patients (group B) had amino acids infused for 2 h before the onset of anaesthesia. Eight control patients (group C) had corresponding volumes of nutrient-free saline solution infused for 1 h before and the first hour of

---

EVA SELLDÉN, MD (Department of Anaesthesiology); ROBERT BRÄNSTRÖM, BM, TOMAS BRUNDIN, MD, PHD (Department of Clinical Physiology); Karolinska Hospital, S-171 76 Stockholm, Sweden. Accepted for publication: September 5, 1995.

Correspondence to E. S.

Table 1 Mean (SEM or range) data for patient groups A–C and for the volunteer group D

Group	*n*	Age (yr)	Weight (kg)	Height (m)	Calculated basal energy expenditure (W)	Duration of anaesthesia (min)	Duration of surgery (min)
A	8	48 (41–53)	67 (5)	1.66 (0.02)	66 (3)	144 (9)	90 (7)
B	8	49 (41–60)	64 (2)	1.69 (0.01)	66 (1)	128 (13)	88 (12)
C	8	47 (41–50)	64 (4)	1.63 (0.02)	65 (2)	154 (11)	99 (7)
D	6	50 (42–56)	63 (2)	1.66 (0.03)	65 (3)	—	—

anaesthesia. The six healthy female volunteers (group D) not subjected to premedication or anaesthesia, reported to the laboratory after an overnight fast. They were studied before and over the 4 h after the onset of a 2-h amino acid infusion, identical to that given to the patients (groups A and B). All subjects were informed of the nature, purpose and possible risks of the study before giving consent to participate. The study was reviewed and approved by the institutional Ethics Committee.

The first 16 patients studied were allocated to groups A and C. Otherwise the patients were not randomized. The study was not blinded. Patients in group B, receiving the entire 2-h infusion of amino acids before the onset of anaesthesia were studied later, as was the volunteer group. All patients were prepared according to standard preoperative routines. All studies, including those in the volunteers, were started at 07:30 after an overnight fast of 12–14 h. At 3 h before anaesthesia the patients received oral premedication with lorazepam 1–2 mg. In the patients and volunteers, a thermometer probe was inserted in the rectum 10–15 cm and two arm veins were cannulated. One catheter for amino acid infusion was inserted and advanced centrally, 30 cm, to reach the subclavian vein. A cubital vein of the other arm was cannulated for blood sampling. Except for 1 u. of warmed blood, given to one of the controls during anaesthesia, no warming device was used. The nutrient-free saline infusions (500 ml h^{-1}) were given at room temperature to all patients during operation.

Respiratory gas exchange was measured for 6–10-min periods by continuous breath-by-breath analysis (Medigraphics, System CPX/D, Medical Graphics Corp., St Paul, MN 55127, USA) using a noseclip and mouthpiece technique with which the subjects had been previously familiarized. The apparatus used for gas exchange analysis, periodically controlled in the laboratory for gas flow and gas concentrations, was calibrated for gas flow and concentrations using a 3 litre precision syringe and calibrated gases before each study. During periods of gas collection, the gas flow and concentrations were measured continuously and gas exchange automatically calculated and recorded each 20 s. Frequent recording facilitates immediate detection of a gas leakage, which may occur, especially when collecting expired gas in the early postoperative period.

Before the amino acid or saline infusions were started, baseline measurements were made of temperature, heart rate, arterial pressure and pulmonary gas exchange. Rectal temperature was measured each 1 min, either digitally, as described earlier [16], or with an Exagon thermometer (MC 8700, Roskilde, Denmark) throughout the observation period, that is before, during and after anaesthesia until 4 h after the end of the amino acid infusion for the patients; and before, during and 2 h after the amino acid infusion for the volunteers. After each study, the probes were calibrated with the same precision thermometer. Room temperature was monitored continuously and maintained at 21–23 °C. Blood samples for analysis of free plasma amino acids were obtained twice, at the end of the amino acid–saline infusion and 2 h later.

During recovery from anaesthesia, patients were observed by the same observer for the presence or absence of obvious generalized shivering. Postoperative pain relief was given to all patients after measurement of gas exchange after operation. In Group A, after baseline measurements at 1 h after premedication, a mixture of 19 amino acids (Vamin 18 g N/litre, Pharmacia, Sweden) was infused i.v. at a rate of 126 ml h^{-1}, corresponding to 240 kJ of energy per hour over 2 h. After 60 min of infusion, measurements of pulmonary gas exchange were repeated ("before anaesthesia"), and immediately after that, the patients were anaesthetized. The amino acid infusion then continued during the first hour of anaesthesia. Within 5 min after emergence from anaesthesia, analysis of pulmonary gas exchange was repeated ("after anaesthesia"). Mean duration of anaesthesia in group A was 144 (SEM 9) min and that of surgery 90 (7) min. In group B, patients received an amino acid infusion, identical to that given in group A. However, it was given 2 h before anaesthesia. When the amino acid infusion ceased, measurements of pulmonary gas exchange were repeated ("before anaesthesia"), after which anaesthesia was induced. Within 5 min after the end of anaesthesia, analysis of pulmonary gas exchange was repeated ("after anaesthesia"). In group B, mean duration of anaesthesia was 128 (13) min and that of surgery 88 (12) min. In group C, control patients were treated in the same manner as group A, but they received equal volumes of nutrient-free Ringer's solution instead of amino acids for 1 h before anaesthesia and during the first hour of anaesthesia. Pulmonary gas exchange measurements were performed and repeated as in group A. In group C the duration of anaesthesia was 154 (11) min and that of surgery 99 (7) min. Differences in duration of anaesthesia and surgery represent the time necessary for the routine procedures of anaesthesia and pre-surgical preparation of the patients. In group D, healthy volunteers were studied in the morning after an overnight fast and 30 min rest in the laboratory. After baseline measurements they received a 2-h amino acid infusion identical to that given to patients in groups A and B. Measurements were then repeated every 30 min until 2 h after the end of the amino acid infusion.

The dose of the amino acid mixture, 240 kJ h^{-1}, was identical to that given during operation in our earlier study of anaesthetized patients [15].

Anaesthesia was the same in all patients and comprised induction with thiopentone 5 mg kg^{-1} and maintenance with 1–2 % enflurane and 60 % nitrous oxide in oxygen using an Engström ventilator 2000 (Gambro Engström AB, Bromma, Sweden). All patients were monitored with pulse oximetry and capnography (Datex, Sweden). Neuromuscular block, monitored by a train-of-four technique [17], was produced with a bolus dose of atracurium 0.5 mg kg^{-1} followed by a continuous infusion of 0.5 mg kg^{-1} h^{-1}. Fentanyl 3 μg kg^{-1} was given before surgery. Atracurium infusion was terminated 0.5 h before the expected end of operation, and residual neuromuscular block was antagonized with neostigmine 2.5 mg together with atropine 0.5 mg immediately after the end of surgery. Heart rate was recorded from the electrocardiogram and arterial pressure determined by sphygmomanometry at 5-min intervals.

Energy expenditure was calculated from pulmonary gas exchange [18, 19]. Free plasma amino acids were separated by high-pressure liquid chromatography and analysed fluorimetrically using a fluorescence HPLC monitor (RF-535, Shimadzu, Tokyo, Japan). Standard statistical methods were used. For comparison between groups, data were first analysed by repeated measures ANOVA and differences then calculated by *post hoc* testing [20]. Within-group differences between baseline and later measurements were calculated using the *t* test for paired observations. Data in the text, tables and figures are given as mean (SEM).

Results

RECTAL TEMPERATURE

Baseline rectal temperatures were 36.88 (0.07) °C in patient groups A–C and 36.65 (0.10) °C in the volunteer group D (ns) (tables 2, 3). During the first hour of amino acid infusion, rectal temperature increased significantly from the basal state, by 0.20 (0.04) °C ($P < 0.001$) in the volunteers and by 0.23 (0.07) °C and 0.38 (0.09) °C in patient groups A and B, respectively (tables 2, 3, figs 1, 2). In control patients (group C), it did not change during the 1-h pre-anaesthesia infusion of saline. After 2 h of amino acid infusion, the temperature increase was 0.35 (0.04) °C in volunteers and 0.60 (0.09) °C in group B ($P < 0.05$) (tables 2, 3, fig. 3). Onset of anaesthesia caused immediate temperature reductions in all patients. During the first 30 min of anaesthesia, it decreased by 0.34 (0.04) °C in group A, 0.48 (0.10) °C in group B and 0.44 (0.07) °C in control patients (group C) (fig. 1). In group B, receiving the entire amino acid infusion before anaesthesia the initial decrease in rectal temperature closely followed that of the controls, with a steep reduction of 0.94 (0.16) °C during the first hour of anaesthesia (fig. 1).

Table 2. Rectal temperature, pulmonary oxygen uptake, respiratory exchange ratio, whole body energy expenditure and heart rate of the six healthy female volunteers (group D) studied before, during and after a 2-h period of i.v. infusion of amino acids, 240 kJ h^{-1} (mean (SEM)). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with baseline

	Time during amino acid infusion (min)			Time after amino acid infusion (min)			
Baseline	60	90	120	30	60	90	120
Rectal temperature (°C) 36.65 (0.10)	36.83 (0.12)***	36.92 (0.11)***	37.00 (0.12)***	37.07 (0.11)***	37.15 (0.11)***	37.15 (0.11)***	37.13 (0.11)***
Pulmonary oxygen uptake (ml min^{-1}) 196 (8)	234 (9)***	229 (10)***	235 (8)***	232 (10)***	226 (10)***	217 (8)***	217 (10)***
Respiratory exchange ratio 0.79 (0.02)	0.82 (0.01)	0.82 (0.02)	0.81 (0.01)	0.78 (0.02)	0.75 (0.0)*	0.77 (0.02)	0.74 (0.02)**
Energy expenditure (W) 66 (3)	79 (3)***	77 (3)***	79 (2)***	78 (3)***	75 (3)***	72 (3)**	72 (3)**
Heart rate (beat min^{-1}) 63 (1)	64 (1)*	64 (1)*	66 (2)*	67 (2)*	67 (2)*	67 (1)*	68 (1)*

Table 3 Rectal temperature, pulmonary oxygen uptake, respiratory exchange ratio, energy expenditure, pulmonary ventilation and heart rate measured 1 h after premedication ("baseline"), during amino acid–saline infusion before the onset of anaesthesia (before anaesthesia) and on awakening (after anaesthesia) (mean (SEM)). Group A = eight patients receiving amino acids for 1 h before the onset of anaesthesia and 1 h of anaesthesia; group B = eight patients receiving amino acids for 2 h before the onset of anaesthesia; and group C = eight control patients receiving saline solution for 1 h before the onset of anaesthesia and for 1 h of anaesthesia. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with baseline

Duration of amino acid infusion:	Baseline	Before anaesthesia 1 h	Before anaesthesia 2 h	After anaesthesia
Rectal temperature (°C)				
Group A	37.09 (0.05)	37.37 (0.06)***	—	37.14 (0.27)
Group B	36.69 (0.10)	37.06 (0.09)***	37.28 (0.07)***	36.49 (0.15)
Group C	36.98 (0.14)	37.00 (0.15)	—	35.98 (0.12)*
Pulmonary oxygen uptake (ml min^{-1})				
Group A	179 (10)	213 (18)	—	264 (19)***
Group B	175 (10)	—	209 (13)	277 (43)*
Group C	166 (7)	164 (8)	—	193 (24)
Respiratory exchange ratio				
Group A	0.79 (0.01)	0.82 (0.01)*	—	0.80 (0.01)
Group B	0.79 (0.003)	—	0.83 (0.01)*	0.81 (0.01)
Group C	0.80 (0.01)	0.78 (0.01)	—	0.80 (0.01)
Energy expenditure (W)				
Group A	59 (3)	72 (6)*	—	88 (7)***
Group B	59 (3)	—	71 (4)***	94 (15)*
Group C	56 (2)	55 (3)	—	63 (4)
Pulmonary ventilation (litre min^{-1})				
Group A	5.4 (0.3)	6.2 (0.4)*	—	7.4 (0.6)**
Group B	5.7 (0.4)	—	6.4 (0.4)	8.5 (1.1)*
Group C	5.5 (0.5)	5.0 (0.5)	—	5.5 (0.4)
Heart rate (beat min^{-1})				
Group A	67 (4)	76 (3)	—	80 (5)*
Group B	69 (4)	—	76 (4)	76 (2)
Group C	74 (6)	74 (4)	—	84 (4)

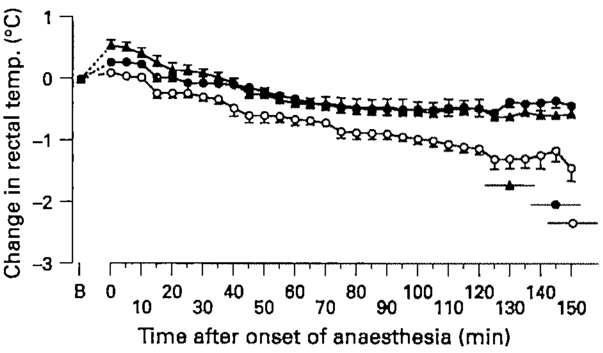


Figure 1 Changes in rectal temperature from baseline measurements (B) throughout anaesthesia in eight patients receiving amino acid infusion for 1 h before and 1 h of anaesthesia (●), eight patients receiving amino acids for 2 h before anaesthesia (▲) and eight patients receiving a nutrient-free saline solution for 1 h before and 1 h of anaesthesia (○). Vertical bars = SEM of mean changes, horizontal bars = SEM of awakening time.

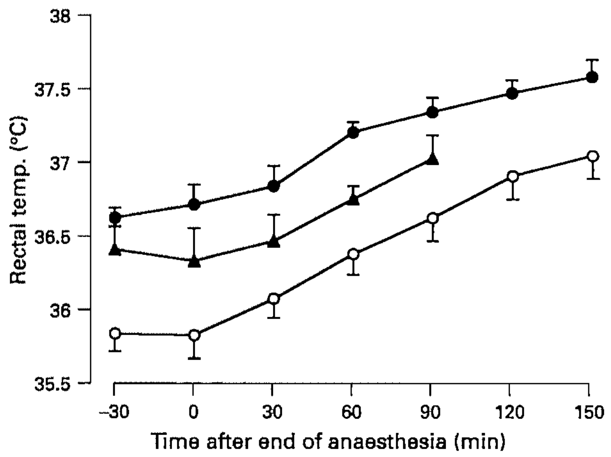


Figure 2 Rectal temperature in absolute terms measured after the end of anaesthesia. Patient groups and symbols as in figure 1.

However, the decrease in temperature from the onset of anaesthesia was significantly greater in the control group than in both the amino acid treated groups throughout anaesthesia. At awakening after 144 (9) and 128 (13) min of anaesthesia in groups A and B, respectively, the temperature decline had not reduced the temperatures to levels significantly below baseline values. When the control patients awakened after 154 (11) min of anaesthesia, mean temperature was 1.00 (0.08) °C below the baseline level ($P < 0.01$) (table 3, fig. 2). This group required approximately 100 min in postoperative recovery to return to baseline temperature levels (fig. 2). In the volunteers, not subjected to premedication or anaesthesia, rectal temperature increased by 0.35 (0.04) °C during infusion and continued to increase for 90 min after the amino acid infusion ceased and remained at its maximum when the study ended (table 2, fig. 3).

PULMONARY OXYGEN UPTAKE

Baseline oxygen consumption did not differ significantly between the patient groups (table 3). Baseline values for oxygen consumption in the volunteers (196 (8) ml min^{-1}) did not differ from those in the

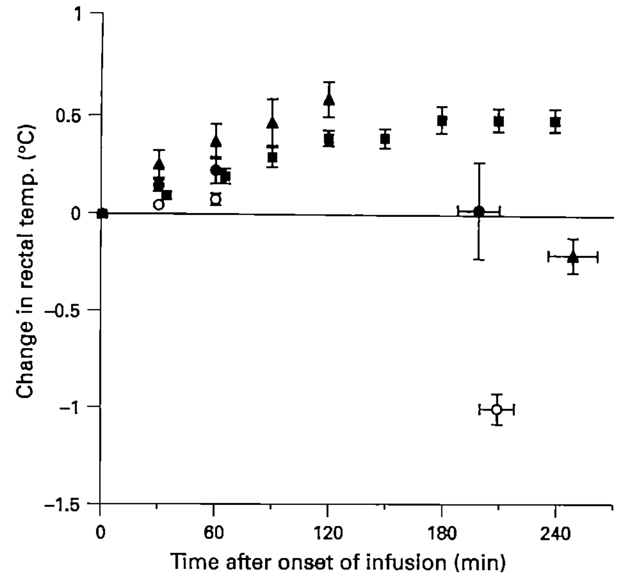


Figure 3 Changes in rectal temperature from onset of i.v. amino acid–saline infusion in eight patients receiving an amino acid infusion for 1 h before and 1 h of anaesthesia (●), eight patients receiving amino acids for 2 h before anaesthesia (▲), eight patients receiving a nutrient-free saline solution for 1 h before and 1 h of anaesthesia (○) and six unanaesthetized volunteers, receiving identical amino acid infusions for 2 h (■). Vertical bars = SEM of mean changes, horizontal bars = SEM of awakening time.

amino acid treated groups (A and B). After 1 h of preoperative amino acid infusion, pulmonary oxygen uptake had increased by 34 (12) ml min^{-1} in group A, and by 38 (3) ml min^{-1} in the volunteers (group D) (ns). After 2 h of preoperative amino acid infusion, oxygen uptake had increased by 34 (6) ml min^{-1} in group B, which was not different from that in group D (39 (5) ml min^{-1}) (tables 2, 3). In the controls (group C), oxygen uptake did not change from its baseline level during the 1-h pre-anaesthesia saline infusion (table 3).

At awakening, oxygen uptake increased to 85 (15) ml min^{-1} ($P < 0.001$) and 102 (45) ml min^{-1} ($P < 0.05$) above baseline in groups A and B, respectively. In group C, oxygen uptake did not significantly exceed baseline at awakening (table 3).

In the volunteer group D, maximum oxygen consumption was observed when the amino acid infusion ceased, and after that it decreased continuously. At 2 h after the end of infusion, it was still 21 (4) ml min^{-1} higher than in the basal state ($P < 0.01$) (table 2).

RESPIRATORY EXCHANGE RATIO

Baseline respiratory exchange ratio did not differ significantly between groups (tables 2, 3). In groups A and B the amino acids caused small but significant increases of 0.03 (0.01) ($P < 0.05$) and 0.04 (0.01) ($P < 0.05$), respectively. In the controls, no changes occurred. At awakening, there were no significant differences between patient groups (table 3). In volunteers, the respiratory exchange ratio did not change significantly during the amino acid infusion. However, it decreased gradually after the amino acid infusion ceased and at the end of the study was significantly lower than in the basal state (table 2).

ENERGY EXPENDITURE

Energy expenditures measured at 1 h after premedication were significantly below basal values, calculated from body dimensions and age [21] in all the patients (table 1). The differences were −9.5 (2) % ($P < 0.01$) in group A, −11.5 (4) % ($P < 0.05$) in group B and −15 (3) % ($P < 0.01$) in group C. In the untreated volunteers (group D), basal energy expenditure did not differ significantly from calculated basal values (table 2). As the changes in respiratory exchange ratio were relatively small, the changes in total energy expenditure closely followed those of pulmonary oxygen uptake. In group A it increased by 13 (4) W during 1 h of amino acid infusion, and in group B the increase after 2 h of infusion was 12 (2) W. In the control patients, energy expenditure remained essentially unchanged throughout the observation period (table 3). In the volunteers it increased during the 2-h amino acid infusion by 14 (1) W and remained significantly higher than the baseline measurements at 2 h after infusion (table 2). At awakening from anaesthesia, energy expenditure increased significantly to 88 (6) and 94 (15) W, 49 (10) and 59 (25) % above baseline levels in groups A and B, respectively.

PULMONARY VENTILATION

Baseline pulmonary ventilation was 5.4 (0.3) litre min^{-1} and 5.7 (0.4) litre min^{-1} in the amino acid treated groups A and B, respectively, and did not differ significantly from that in the control group C (5.5 (0.6) litre min^{-1}) (table 3). During the 1-h amino acid infusion before anaesthesia, it increased by 0.8 (0.2) litre min^{-1} in group A ($P < 0.05$). In group B, 2 h of pre-anaesthesia amino acid infusion increased ventilation by 0.7 (0.2) litre min^{-1} ($P < 0.05$). In the control patients, pulmonary ventilation did not change from baseline. At awakening, ventilation increased significantly by approximately 37 % and 49 % in groups A and B, respectively. In the control patients, ventilation was unchanged at awakening (table 3).

HEART RATE AND ARTERIAL OXYGEN SATURATION

At emergence from anaesthesia, heart rate significantly exceeded baseline levels in groups A and C. In the volunteers, heart rate was slightly but significantly higher than basal levels during and after amino acid infusion. Arterial oxygen saturation was unchanged during the study in all patients, being consistently 97–99 %.

SHIVERING

Shivering occurred at awakening after anaesthesia in all control patients, but in none of the patients in group A. In group B, two patients shivered after anaesthesia.

PLASMA CONCENTRATION OF FREE AMINO ACIDS

The control patients (group C) had normal plasma concentrations for the 21 amino acids analysed [22] after 1 h of anaesthesia, and also 2 h later. In groups

Table 4 Plasma concentrations (μmol litre^{-1}) of amino acids in eight patients receiving amino acid infusion for 1 h before and 1 h of anaesthesia (A), in eight patients receiving amino acids for 2 h before anaesthesia (B), in eight control patients receiving saline solution (C) and in six female volunteers (D). Measurements at the end of amino acid infusion and 2 h later (mean (SEM)). *$P < 0.05$, **$P < 0.01$, ***$P < 0.01$ compared with values after the end of infusion

	At end of infusion				2 h later			
Group	A	B	C	D	A	B	C	D
Aspartate	26 (4)	15 (4)	14 (1)	16 (3)	11 (1)***	3 (0)*	21 (1)***	7 (4)
Glutamate	126 (11)	59 (5)	71 (8)	70 (10)	35 (6)***	39 (12)***	44 (11)***	46 (17)***
Asparagine	30 (2)	32 (2)	39 (3)	39 (3)	24 (1)***	31 (2)***	41 (4)***	32 (3)***
Serine	252 (10)	168 (20)	124 (8)	232 (30)	117 (11)***	116 (11)***	118 (11)***	136 (18)***
Glutamine	583 (12)	740 (112)	539 (34)	649 (37)	479 (53)***	723 (11)***	563 (56)***	588 (42)***
Histidine	176 (12)	139 (31)	72 (5)	210 (40)	73 (9)***	77 (2)***	77 (9)***	122 (25)***
Glycine + threonine + citrulline	804 (32)	537 (73)	345 (45)	892 (133)	354 (45)***	382 (27)***	359 (21)***	518 (73)***
Taurine	237 (27)	102 (36)	78 (8)	70 (8)	96 (18)***	82 (20)***	77 (7)***	47 (2)***
Arginine	195 (104)	140 (46)	59 (5)	258 (66)	53 (10)***	64 (11)**	58 (5)***	98 (6)**
Alanine	582 (73)	458 (104)	225 (24)	740 (30)	292 (39)***	325 (25)***	281 (39)***	353 (69)***
Tyrosine	52 (4)	55 (4)	40 (5)	62 (5)	34 (4)***	43 (3)***	41 (6)***	49 (4)***
α-Aminobutyrate	38 (3)	36 (3)	20 (1)	38 (5)	31 (4)***	33 (3)***	19 (2)***	37 (4)***
Methionine	133 (7)	87 (21)	14 (1)	143 (23)	40 (5)***	37 (3)***	17 (1)***	72 (20)***
Valine	550 (34)	412 (55)	185 (19)	540 (60)	297 (35)***	302 (20)***	191 (22)***	399 (51)***
Phenylalanine	174 (13)	122 (16)	49 (3)	173 (23)	71 (8)***	60 (12)***	52 (3)***	173 (23)***
Isoleucine	213 (14)	115 (20)	49 (4)	171 (27)	85 (10)***	68 (4)***	56 (3)***	97 (25)***
Leucine	311 (20)	186 (26)	101 (10)	259 (39)	140 (16)***	125 (7)***	113 (10)***	160 (31)***
Ornithine	96 (9)	103 (10)	50 (7)	112 (10)	53 (6)***	66 (11)***	51 (11)***	90 (18)***
Lysine	316 (18)	256 (42)	130 (11)	406 (60)	102 (14)***	148 (8)***	135 (14)***	220 (54)***

A, B and D, plasma concentrations for most of the amino acids were significantly above normal immediately after the 2 h amino acid infusions, and higher than in the control patients; the sums of the amino acid concentrations were 4.84, 3.74, 2.21 and 4.96 mmol litre^{-1} groups A, B, C and D, respectively (table 4). In group B, premedicated, and receiving the entire infusion before the onset of anaesthesia, there was a significantly lower maximum sum of amino acid concentrations than the two other amino acid treated groups (A and D) ($P < 0.05$). This difference resulted from significantly reduced concentrations of the individual amino acids, glutamate, arginine, methionine, isoleucine and leucine. Glutamine tended to be higher only in group B compared with the other amino acid treated groups, and remained so 2 h after infusion. Immediately after infusion, the concentration of taurine was significantly higher in group A than in all of the other groups.

At 2 h after the amino acid infusions, individual amino acid concentrations were essentially similar in groups A, B and D, and only moderately increased compared with those in the control patients (group C). The sums of the amino acid concentrations were 2.39, 2.72, 2.31 and 3.17 mmol litre^{-1} in groups A, B, C and D, respectively (ns).

Discussion

Recently, we demonstrated that the thermic effect of amino acids is augmented during general anaesthesia, and that peroperative amino acid infusion thereby prevents the anaesthesia-induced reduction in metabolism and the accompanying postoperative hypothermia [15]. The present data confirm these findings and in addition suggest that amino acid infusion counteracts postoperative hypothermia when given, entirely or partly, before anaesthesia. The anti-hypothermic effect resulted from both increased preoperative heat accumulation and delayed metabolic stimulation immediately after anaesthesia. In addition, heat accumulation in response to amino acids infusion after premedication with lorazepam was greater than normal. Thus when started 1 h after lorazepam premedication, the amino acid infusion increased patients' rectal temperature by approximately 0.3 °C h^{-1}, an increase twice that observed in the volunteers subjected to identical amino acid infusions but not premedicated. This implies that premedication with lorazepam augmented selectively the accumulated part of the extra heat produced during amino acid administration. To our knowledge this response to lorazepam administration has not been reported before. In addition, patients receiving amino acid infusions for 2 h before anaesthesia or for 1 h before and 1 h of anaesthesia exhibited an increase in oxidative metabolism at awakening after anaesthesia of up to 50–60 % above baseline values (before anaesthesia). In the control patients, similarly premedicated and anaesthetized, but receiving saline instead of amino acids, energy expenditure did not increase significantly above baseline, despite vigorous shivering at awakening. Thus the ability of delayed metabolic stimulation, similar to that described recently at awakening immediately after peroperative amino acid infusions [15], was demonstrable also at awakening 30–90 min after the end of amino acid infusions.

Shivering was observed in two of the patients receiving the 2-h amino acid infusion before anaesthesia, but in none of those who had received the infusion for 1 h before and 1 h of anaesthesia. This indicates that prevention of hypothermia was more effective when a peroperative period of infusion was included. This was illustrated further by the finding that the initial decrease in temperature during the first 30 min of anaesthesia was prevented to a significantly greater extent, although not abolished, in patients receiving half of the infusion during anaesthesia. In those patients receiving the entire amino acid infusion before the onset of anaesthesia, the initial temperature change did not differ significantly from that in the control patients receiving saline. However, the considerable amounts of heat accumulated during the 2-h pre-anaesthesia amino acid infusion raised these patients' pre-anaesthesia temperatures to levels which prevented the temperature from reaching true hypothermic levels after operation.

Thus the decrease in temperature during the initial phase of anaesthesia, probably reflecting redistribution of heat within the body [23, 24], was not prevented by pre-anaesthetic infusions of amino acids, and prevented only partly in those patients in whom the infusions were continued during the first hour of anaesthesia. These results confirm our recent finding that peroperative amino acids could not significantly reduce the decrease in temperature until 20 min after the onset of anaesthesia [15].

It is not immediately obvious why amino acid-induced heat accumulation should increase after premedication with lorazepam. Administration of benzodiazepines may interfere with central thermoregulatory control that normally limits the amino acid-induced upward regulation of the resting set point for arterial blood temperature [13–15, 25]. The finding of a significantly reduced resting energy expenditure in all patient groups 1 h after lorazepam is consistent with other reports of reduced metabolism after administration of benzodiazepines [26, 27]. However, the present data indicate that the thermic effect of amino acids was not quantitatively affected, although baseline energy expenditure was depressed by lorazepam.

At awakening, vigorous, generalized shivering occurred in all control patients not receiving amino acids. In spite of the shivering, oxygen consumption was not significantly higher than baseline levels. This finding, similar to that in our previous study [15], confirms that, compared with delayed amino acid-induced thermogenesis, generalized shivering is a relatively weak stimulator of prompt increments in whole body oxidative metabolism in the early postoperative phase.

In awake volunteers, energy expenditure reached its maximum at the end of the 2-h amino acid infusion and then declined slowly. Heat accumulation, however, continued throughout the post-infusion observation period, maximum temperatures being recorded 60–90 min after the infusion. Thus the heat accumulation response to a 2-h amino acid infusion continued for a prolonged period, significant hyperthermia being evident for more than 2 h after the infusion. In patients receiving amino acids before or partly during anaesthesia, postoperative temperatures remained significantly higher than in the control patients during the entire postoperative observation period.

The present findings illustrate that the development of the postoperative hypothermia may be related to anaesthesia-induced suppression of heat production rather than increased heat elimination. The present results indicate that the mechanisms for increased thermogenesis and heat accumulation, when elicited by amino acids, are able to restart after an anaesthesia-induced intermission.

Pulmonary ventilation increased significantly on awakening from anaesthesia in the amino acid treated patients, but not in the control patients. As in our previous study [15], oxygen saturation was normal, indicating that increased oxygen consumption was accompanied by a corresponding increase in ventilation.

In the premedicated patients but not in the volunteers, respiratory exchange ratio increased slightly during amino acid infusion. In male volunteers receiving similar amino acid infusions in earlier studies, the respiratory exchange ratio did not change [14]. It seems difficult to judge if this significant difference represents a true pharmacological effect of lorazepam.

Plasma amino acid concentrations were significantly lower in patients receiving the entire amino acid infusion before anaesthesia compared with those in whom the infusions continued during the first hour of anaesthesia. This might indicate that amino acids infused after the onset of anaesthesia are consumed by the tissues to a lesser extent than those infused before the onset of anaesthesia. However, the sum of the concentrations of all free amino acids was significantly lower also compared with that in volunteers. This might suggest that premedication *per se* could have increased tissue consumption of free amino acids, but additional studies are needed to elucidate this. A significant reduction in plasma concentrations of free amino acids during surgery has been described previously [28].

Anaesthesia-induced postoperative hypothermia is a considerable clinical problem [29] and the present findings may have clinical potential. In suitable patients, i.v. infusion of an amino acid mixture before and during the beginning of anaesthesia for elective and acute surgery is an easy method of preventing anaesthesia-induced hypothermia. Furthermore, compared with the methods of treating hypothermia after operation [30, 31], prevention with amino acids might be beneficial from a metabolic point of view. It has been shown that successful prevention of the development of anaesthesia-induced hypothermia with warming devices, combined with high operating room temperatures, also prevents negative nitrogen balance and catabolism in the postoperative period [3, 31]. Further studies are needed to establish if postoperative nitrogen balance is affected also when the development of postoperative hypothermia is prevented by means of amino acid administration.

The use of amino acids for prevention of anaesthesia-induced hypothermia cannot be recommended for all patients. Treatment should be limited strictly to those who can cope with the possible side effects of an amino acid load. It may be hazardous or harmful for patients with hepatic, renal or metabolic diseases, and should be avoided also in patients with cardiopulmonary insufficiency, who may be unable to cope with the enhanced demands for ventilation and gas transport that occur on awakening. In addition, it should of course be avoided in children < 15 yr until tolerance studies have been performed. With these caveats, amino acid treatment might be a clinically useful and safe method for counteracting the development of anaesthesia-induced hypothermia and its postoperative complications.

Acknowledgements

This study was supported by the Swedish Medical Research Council, project No. 3108, Magnus Bergwalls stiftelse, Pharmacia Hospital Care and Svenska Sällskapet för Medicinsk Forskning.

References

1. Valeri CR, Feingold H, Cassidy G, Ragno G, Khuri S, Altschule MD. Hypothermia-induced reversible platelet dysfunction. *Annals of Surgery* 1987; **205**: 175–181.
2. Heier T, Caldwell JE, Sessler DI, Miller RD. Mild intraoperative hypothermia increases duration of action and spontaneous recovery of vercuronium blockade during nitrous oxide-isoflurane anesthesia in humans. *Anesthesiology* 1991; **74**: 815–819.
3. Carli F, Emery P, Freemantle CAJ. Effect of peroperative normothermia on postoperative protein metabolism in elderly patients undergoing hip arthroplasty. *British Journal of Anaesthesia* 1989; **63**: 276–282.
4. Scheffield CW, Sessler DI, Hunt KH. Mild hypothermia during isoflurane anaesthesia decreases resistance to E. coli dermal infection in guinea pigs. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 201–205.
5. Hynson JM, Sessler DI, Moayeri A, McGuire J, Schroeder M. The effects of pre-induction warming on temperature and blood pressure during propofol/nitrous oxide anesthesia. *Anesthesiology* 1993; **79**: 219–228.
6. Just B, Trévien V, Delva E, Lienhart A. Prevention of intraoperative hypothermia by preoperative skin–surface warming. *Anesthesiology* 1993; **79**: 214–218.
7. Sessler DI. Central thermoregulatory inhibition by general anesthesia. *Anesthesiology* 1991; **75**: 557–559.
8. Roe CF. Temperature regulation in anaesthesia. In: Hardy JD, Gagge AP, Stolwijk JAJ, eds. *Physiological and Behavioral Temperature Regulation*. Springfield, IL: Charles C. Thomas, 1970; 727–740.
9. Hemingway A. The effect of barbital anesthesia on temperature regulation. *American Journal of Physiology* 1941; **134**: 350–358.
10. Jéquier E. The influence of nutrient administration on energy expenditure in man. *Clinical Nutrition* 1986; **5**: 181–186.
11. Brundin T, Wahren J. Effects of i.v. amino acids on human splanchnic and whole-body oxygen consumption, blood flow and blood temperature in healthy subjects. *American Journal of Physiology* 1994; **266**: E396–E402.
12. Aksnes A-K, Brundin T, Wahren J. Metabolic, thermal and circulatory effects of intravenous infusion of amino acids in tetraplegic patients with complete spinal cord lesions. *Clinical Physiology* 1995; **15**: 377–396.
13. Brundin T, Wahren J. Influence of protein ingestion on human splanchnic and whole-body oxygen consumption, blood flow, and blood temperature. *Metabolism* 1994; **43**: 626–632.
14. Brundin T, Wahren J. Renal oxygen consumption, thermogenesis, and amino acid utilization during i.v. infusion of amino acids in man. *American Journal of Physiology* 1994; **267**: E648–E655.
15. Selldén E, Brundin T, Wahren J. Augmented thermic effect of amino acids under general anaesthesia. A mechanism useful for prevention of anaesthesia-induced hypothermia. *Clinical Science* 1994; **86**: 611–618.
16. Kilbom Å, Brundin T. Circulatory effects of isometric muscle contractions, performed separately and in combination with dynamic exercise. *European Journal of Applied Physiology* 1976; **36**: 7–17.
17. Viby-Mogensen J. Clinical assessment of neuromuscular transmission. *British Journal of Anaesthesia* 1982; **54**: 209–223.
18. Lusk G. Animal calorimetry. Twenty-fourth paper. Analysis of the oxidation of mixtures of carbohydrates and fat. A correction. *Journal of Biological Chemistry* 1924; **59**: 41–42.
19. Zunz N, Schumburg NAEF. In: Hirschwald A, ed. *Studien zu einer Physiologie des Marsches*. Berlin, 1901.
20. Scheffé HA. A method for judging all contrasts in the analysis of variance. *Biometrika* 1953; **40**: 87–104.
21. Harris JA, Benedict FG. *A Biometric Study of Basal Metabolism in Man*. Washington DC: Carnegie Institution of Washington, 1919; Publication No. 279.
22. Schmitz JE. Infusions- und Ernährungstherapie des Polytraumatisierten. In: Bergmann H, ed. *Anaesthesiology and Intensive Care Medicine*. Berlin, Heidelberg: Springer-Verlag, 1985.
23. Holdcroft A, Hall GM, Cooper GM. Redistribution of body heat during anaesthesia. *Anaesthesia* 1979; **34**: 758–764.
24. Frank SM, Yoram S, Srinivasa NR, Fleisher LA, Beattle C. Core hypothermia and skin–surface temperature gradients. *Anesthesiology* 1994; **80**: 502–508.
25. Brundin T, Thörne A, Wahren J. Heat leakage across the abdominal wall and meal-induced thermogenesis in normal weight and obese subjects. *Metabolism* 1992; **41**: 49–55.
26. Kirvelä O, Katila A, Aantaa R, Kanto J, Himberg JJ. Metabolic and subjective responses to oral diazepam and midazolam. *European Journal of Anaesthesiology* 1994; **11**: 365–369.
27. Weyland W, Bräuer A, Weyland A, Janitzki AS, Braun U. Der einfluss von Sedierung auf die Sauerstoffaufnahme unter Spontanatmung. *Anaesthetist* 1993; **42**: 391–395.
28. Lund J. Amino acid metabolism during upper abdominal surgery (dissertation). *Acta Universitatis Upsaliensis* 1985; 1–27.
29. Flacke JW, Flacke WE. Inadvertent hypothermia: Frequent, insidious and often serious. *Seminars in Anesthesia* 1983; II: 183–196.
30. Henneberg S, Eklund A, Joakimsson PO, Stjärnström H, Wiklund L. Effects of a thermal ceiling on postoperative hypothermia. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 602–606.
31. Carli F, Gabrielczyk M, Clark MM, Aber VR. An investigation of factors affecting postoperative rewarming of adult patients. *Anaesthesia* 1986; **41**: 363–369.

British Journal of Anaesthesia 1996; 76: 235–238

Time course of potentiation of mivacurium by halothane and isoflurane in children

O. A. MERETOJA, K. WIRTAVUORI, T. TAIVAINEN AND K. T. OLKKOLA

Summary

We studied 40 children, aged 1–15 yr, to analyse the time course of potentiation of mivacurium produced by halothane and isoflurane. A steady infusion requirement of mivacurium to maintain 90% neuromuscular block was established during thiopentone–alfentanil–nitrous oxide–oxygen anaesthesia. Patients were then allocated randomly to receive 1 MAC end-tidal concentration of either halothane (group Hal) or isoflurane (group Iso) while neuromuscular block was maintained at 90%. Both volatile agents decreased the infusion requirements of mivacurium in an exponential manner in that maximal potentiation occurred only after 30–80 min. Maximal reduction in infusion rate (32% in group Hal and 70% in group Iso; $P < 0.0001$) did not depend on the age of the child but became established sooner the younger the child in the case of isoflurane ($P = 0.002$). (*Br. J. Anaesth.* 1996; **76**: 235–238)

Key words

Anaesthetics volatile, halothane. Anaesthetics volatile, isoflurane. Neuromuscular block, mivacurium. Pharmacodynamics.

Volatile anaesthetic agents reduce the dose requirements of non-depolarizing neuromuscular blocking agents by 0–70% [1–6]. This effect may depend not only on the particular volatile anaesthetic but also on the neuromuscular blocking agent [2, 3]. The potentiation may be a time-dependent phenomenon, even though there are conflicting results [7–9]. In some early studies on the potentiation of neuromuscular blockers by volatile anaesthetic agents, the investigators maintained a steady anaesthetic concentration for more than 1 h before administering the neuromuscular blocker [1], whereas in some recent studies volatile agents were given for less than 15 min [6, 10–12]. This difference in timing may have greatly affected the results of these studies. We designed a study to evaluate the time course of potentiation of mivacurium by halothane and isoflurane in children in order to clarify the issue and to find if the age of the paediatric patient affected the magnitude or time course of this potentiation. Mivacurium was used as the neuromuscular blocker because of its short elimination half-life.

Patients and methods

The study was approved by the Ethics Committee of the Children's Hospital University of Helsinki. After obtaining parental informed consent, we studied 40 ASA I–II patients, aged 1–15 yr. Patients were undergoing elective orthopaedic or general surgery with minimal blood loss and with an anticipated duration of at least 2 h. Patients had no disease or medication known to affect neuromuscular function.

Premedication comprised oral midazolam 0.4–0.5 mg kg^{-1} (maximum dose being 15 mg), 30–60 min before induction. Anaesthesia was induced with thiopentone 4–6 mg kg^{-1} i.v. and alfentanil 50–100 µg kg^{-1} i.v., and inhalation of 66% nitrous oxide in oxygen. The trachea was intubated without the use of neuromuscular blocker. Anaesthesia was maintained with an infusion of alfentanil 100 µg kg^{-1} h^{-1} and 66% nitrous oxide in oxygen. End-tidal carbon dioxide was maintained at 5.0–5.5 kPa and core temperature at > 36 °C throughout the study. For peroperative fluid management, Ringer's solution was infused at a rate of 3–4 ml kg^{-1} h^{-1}. Patients did not require any volume replacement for blood loss.

Neuromuscular function was recorded as an adductor pollicis EMG evoked by supramaximal 2 Hz train-of-four responses at 20-s intervals (Relaxograph, Datex, Finland). The stimulating surface electrodes were attached over the ulnar nerve at the wrist, and the forearm was supported on a dorsal splint with the thumb abducted with a tape. Recording electrodes were attached on the adductor pollicis muscle and on the proximal volar surface of the index finger [13]. Palmar skin temperature was measured and maintained above 34 °C with a warming cover. Routine patient monitoring consisted of ECG, non-invasive arterial pressure, pulse oximetry, end-tidal carbon dioxide and halothane or isoflurane measurement (Capnomac, Cardiocap, Datex).

After calibration of the EMG device and having reached a stable train-of-four response for a minimum of 5 min, a bolus dose of mivacurium 0.1 mg kg^{-1} was administered i.v. and, if needed, this was followed by a second, similar dose to establish > 95% neuromuscular block (depression of the first EMG response from control in the train-of-four series of responses). When the first EMG response recovered to 10% of control, an adaptive closed-loop computer controlled infusion of mivacurium was

---

O. A. MERETOJA, MD, K. WIRTAVUORI, MD, T. TAIVAINEN, MD, K. T. OLKKOLA, MD, Department of Anaesthesiology, Children's Hospital University of Helsinki, FIN-00290, Helsinki, Finland.
Accepted for publication: October 4, 1995.
Correspondence to O.A.M.

commenced to maintain a steady 90% neuromuscular block [14]. Mivacurium was diluted in physiological saline to a concentration of 0.5–2.0 mg ml^{-1} depending on the patient's body weight. The computer program controlling the infusion pump was based on the patient's theoretical pharmacokinetic–dynamic variables and used continuous feedback information from the EMG monitor to adjust the infusion rate at 20-s intervals [14]. Real-time neuromuscular block, current infusion rate and cumulative amount of mivacurium infused were shown on a computer screen and stored in the computer memory.

After a steady state infusion of mivacurium of at least 30 min, a sealed envelope indicating the patient's group was opened, and either halothane (group Hal) or isoflurane (group Iso) was commenced at an inspiratory concentration of 4–5% and then titrated individually to rapidly achieve and maintain an age-adjusted 1 MAC end-expiratory concentration of the volatile anaesthetic agent [15, 16]. At this time the infusion rate of alfentanil was reduced by 50%. Any change in the infusion rate of mivacurium was calculated by the computer. The results were drawn on paper and the cumulative infusion dose of mivacurium was calculated for every 10-min period before and after the start of the volatile anaesthetic agent.

All between-group comparisons were made by Kruskal–Wallis and Mann–Whitney *U* tests, and the data are presented as median (range). Changes in the individual infusion rates of mivacurium for the 10-min epochs were compared by Friedman's two-way analysis of variance. Influence of age within the study groups was examined by linear regression analysis. $P < 0.05$ was regarded as significant.

Results

Groups were matched for age, body weight, amounts of induction agents, duration of anaesthesia and steady infusion rate of mivacurium before the volatile anaesthetic agent was commenced (table 1). One MAC end-tidal concentration of the volatile agent was reached within 2–4 min from opening of the vaporizer in all patients. Figures 1 and 2 show the

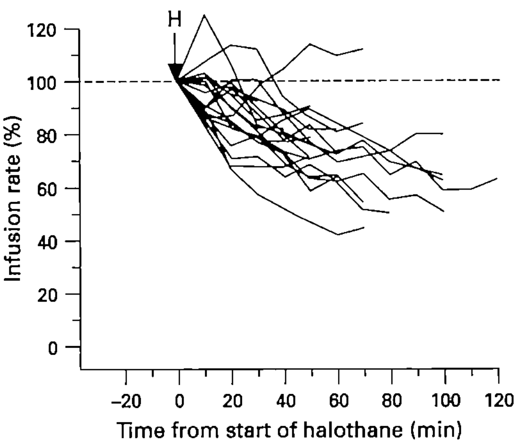


Figure 1 Individual infusion rates of mivacurium at 10-min epochs as a percentage of control from commencement of 1 MAC of end-tidal halothane (H) in children.

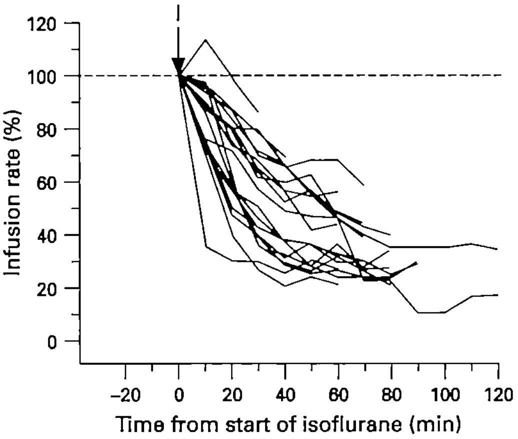


Figure 2 Individual infusion rates of mivacurium at 10-min epochs as a percentage of control from commencement of 1 MAC of end-tidal isoflurane (I) in children.

Table 1 Patient characteristics and mivacurium infusion rates for the study groups (median (range)). *P* values according to Mann–Whitney *U* test

	Group Hal	Group Iso	*P*
Age (yr)	6.4 (1.0–15.5)	7.8 (2.0–14.4)	ns
Body weight (kg)	19.4 (10.6–64.8)	27.7 (9.9–65.0)	ns
Duration of anaesthesia (min)	140 (105–390)	148 (105–330)	ns
Duration of volatile agent (min)	70 (30–200)	70 (37–235)	ns
Infusion rate of mivacurium			
Before volatile agent			
No. of patients	20	20	
μg kg^{-1} min^{-1}	11.0 (6.7–26.3)	12.6 (5.5–25.1)	ns
Percentage of control	100.0	100.0	
30 min after volatile agent			
No. of patients	20	20	
μg kg^{-1} min^{-1}	9.0 (5.4–19.0)	5.8 (2.4–20.1)	< 0.01
Percentage of control	81.9 (57.3–112.0)	54.5 (27.3–86.3)	0.0001
60 min after volatile agent			
No. of patients	13	17	
μg kg^{-1} min^{-1}	7.4 (6.4–10.8)	4.1 (1.7–17.2)	< 0.01
Percentage of control	72.1 (42.2–109.9)	37.0 (22.0–68.3)	0.0001
90 min volatile agent			
No. of patients	5	4	
μg kg^{-1} min^{-1}	6.1 (5.0–10.9)	3.1 (0.7–4.8)	< 0.05
Percentage of control	67.5 (57.0–79.9)	30.3 (11.7–36.1)	< 0.01

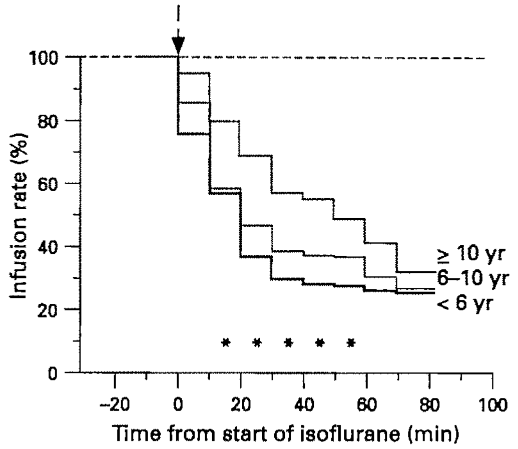


Figure 3 Median infusion rates of mivacurium at 10-min epochs as a percentage of control from commencement of 1 MAC of end-tidal isoflurane (I) in three age groups of children. Potentiation becomes maximal sooner in the youngest children. * $P < 0.05$.

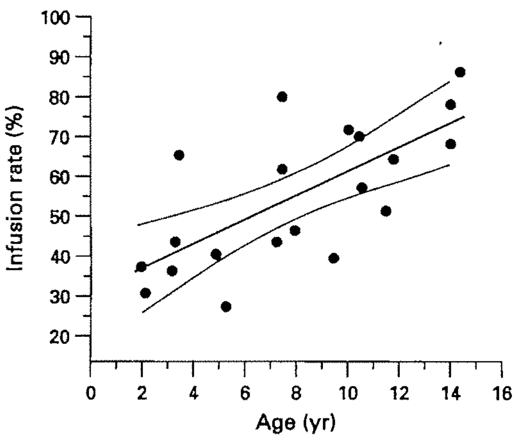


Figure 4 Significant correlation between the age of a child and infusion rate of mivacurium as a percentage of control after 30 min of inhalation of 1 MAC of end-tidal isoflurane. Regression line has been drawn with 95 % confidence intervals ($y = 30+3 \times \text{age}$, $n = 20$, $r = 0.705$, $P = 0.0005$).

individual time course of the effect of halothane and isoflurane on the infusion rate of mivacurium to maintain 90 % neuromuscular block. Within 10 min of inhalation of the selected volatile anaesthetic agent the infusion rate had decreased in group Iso (fig. 2, $P < 0.001$). At all intervals between 10 and 90 min from the start of the volatile anaesthetic, the infusion rate of mivacurium had decreased more in group Iso than in group Hal (table 1).

The maximum effect of halothane or isoflurane in reducing the infusion requirement of mivacurium to maintain 90 % neuromuscular block did not depend on the age of the patient. However, the time course of this potentiation depended on age in group Iso in that maximum potentiation was established sooner the younger the child (time (min) to maximum potentiation $= 32+3 \times \text{age}$ ($r = 0.663$, $P = 0.002$)). Figure 3 illustrates the time course of potentiation of mivacurium by isoflurane in three age groups of children. A similar age-related correlation was not detected in group Hal.

The effect of isoflurane on reducing the requirement for mivacurium was age-dependent within 10–60 min from the start of isoflurane inhalation (r values from 0.515 ($P = 0.02$) to 0.705 ($P < 0.001$)). Figure 4 shows the effect of isoflurane on the infusion requirement of mivacurium in children after 30 min of inhalation of 1 MAC of isoflurane. The younger the child, the smaller was the infusion requirement related to the control 100 % infusion rate before isoflurane (infusion rate (%) $= 30+3 \times \text{age}$ ($r = 0.705$, $P = 0.0005$)). Group Hal did not show similar significant correlations (r values from 0.013 ($P = 0.96$) to 0.227 ($P = 0.34$) within the time interval 10–60 min from the start of halothane inhalation).

Discussion

We have found that potentiation of mivacurium by halothane and isoflurane was strongly time-dependent and took at least 30 min before maximum potentiation was established. In addition, the magnitude of the potentiation did not depend on the age of a child but became established more quickly in younger children when isoflurane was used. We found that conditions for neuromuscular block were unstable for at least the first 30 min of anaesthesia with volatile anaesthesia. This implies that potentiation was decreased with a shorter duration of anaesthesia. Thus it may not be possible to compare data from different studies on neuromuscular blockers if the duration of inhalation anaesthesia is not standardized. Potentiation of mivacurium by isoflurane was greater the younger the child if the duration of anaesthesia was less than 1 h. This suggests that not even a standard duration or concentration of isoflurane guarantees the same degree of potentiation at all ages in children.

There are relatively few studies on the time dependence of the effects of volatile agents on non-depolarizing neuromuscular blockers. Miller, Crique and Eger concluded in 1976 that duration of halothane anaesthesia had no effect on neuromuscular block produced by tubocurarine within 10–160 min [7]. However, their data on cumulative dose–response curves showed that ED_{50} values were greater within 10–20 min than within 40–160 min of halothane anaesthesia (4.6 *vs* 3.1 mg m^{-2}, respectively). Withington and colleagues designed a study with patients as their own controls to evaluate the time course of potentiation of atracurium by enflurane [9]. They found a clear time-dependent reduction in the plasma concentrations of atracurium needed to maintain 90 % neuromuscular block.

We found that halothane and isoflurane produced maximal neuromuscular effect in not less than 30–80 min from onset of administration. Our average infusion rate of mivacurium to maintain 90 % neuromuscular block before the volatile agent was 12 μg kg^{-1} min^{-1} (700 μg kg^{-1} h^{-1}). This rate and its variation are comparable with those described for children to maintain 95 % or 89–99 % neuromuscular block [14, 17, 18]. Brandom and colleagues, and Alifimoff and Goudsouzian found that halothane reduced infusion requirements of mivacurium by 20 % [17, 18]. This reduction in infusion requirements was smaller than that in the present study. However, both of these earlier studies included infusion analysis within the first 15 min of halothane anaesthesia, even though Brandom and colleagues reported that later infusion rates were smaller [18]. Thus it may be that the average infusion rates calculated in these studies did not represent maximal potentiation of neuromuscular block by halothane in children. Our finding of 32% maximal potentiation produced by halothane is very similar to the 36% reduction in vecuronium infusion to maintain 90% neuromuscular block by at least 60 min of halothane anaesthesia in adults [4].

There are no previous paediatric data on infusion requirements for mivacurium during isoflurane anaesthesia. In adults, more than 1 h of isoflurane anaesthesia reduced the bolus dose requirements for tubocurarine by 70% [1] and the infusion requirements for vecuronium to maintain 90% neuromuscular block by 67% [5]. These results for isoflurane-induced potentiation are close to our finding of 70% maximal reduction in infusion requirement of mivacurium during isoflurane anaesthesia. When shorter exposures of isoflurane were studied, less potentiation was observed for mivacurium: 20–30% reduction in dose requirement by 10–15 min of isoflurane [10, 19] and 40% reduction in infusion requirement when infusion data for the first 15 min of isoflurane anaesthesia were included [20]. These results are consistent with our results on the time course of potentiation of mivacurium infusion produced by isoflurane (fig. 2).

A key question in paediatric neuromuscular pharmacology is how infants, children and adults differ in their dose requirements for different neuromuscular blockers [21, 22]. Our study casts doubt on many previous studies on the subject as several studies have been carried out during anaesthesia with unknown duration of volatile anaesthetic agents. Our results indicate that if the timing of the volatile agent has not been controlled, then neuromuscular studies cannot be compared because of unknown potentiation, and comparisons between age groups may be questionable. A serious problem arises if isoflurane has been used; in this case, unstable neuromuscular conditions last for at least 30 min in the youngest children and for even 60 min in older children.

References

1. Miller RD, Eger EI II, Way WL, Stevens WC, Dolan WM. Comparative neuromuscular effects of Forane and halothane alone and in combination with d-tubocurarine in man. *Anesthesiology* 1971; **35**: 38–42.
2. Rupp SM, Miller RD, Gencarelli PJ. Vecuronium-induced neuromuscular blockade during enflurane, isoflurane, and halothane anesthesia in humans. *Anesthesiology* 1984; **60**: 102–105.
3. Rupp SM, McChristian JW, Miller RD. Neuromuscular effects of atracurium during halothane–nitrous oxide and enflurane–nitrous oxide anesthesia in humans. *Anesthesiology* 1985; **63**: 16–19.
4. Swen J, Gencarelli PJ, Koot HWJ. Vecuronium infusion dose requirements during fentanyl and halothane anesthesia in humans. *Anesthesia and Analgesia* 1985; **64**: 411–414.
5. Cannon JE, Fahey MR, Castagnoli KP, Furuta T, Canfell PC, Sharma M, Miller RD. Continuous infusion of vecuronium: the effect of anesthetic agents. *Anesthesiology* 1987; **67**: 503–506.
6. From RP, Pearson KS, Choi WW, Abou-Donia M, Sokoll MD. Neuromuscular and cardiovascular effects of mivacurium chloride (BW B1090U) during nitrous oxide–fentanyl–thiopentone and nitrous oxide–halothane anaesthesia. *British Journal of Anaesthesia* 1990; **64**: 193–198.
7. Miller RD, Crique M, Eger EI II. Duration of halothane anesthesia and neuromuscular blockade with d-tubocurarine. *Anesthesiology* 1976; **44**: 206–210.
8. Stanski DR, Ham J, Miller RD, Sheiner LB. Time-dependent increase in sensitivity to d-tubocurarine during enflurane anesthesia in man. *Anesthesiology* 1980; **52**: 483–487.
9. Withington DE, Donati F, Bevan DR, Varin F. Potentiation of atracurium neuromuscular blockade by enflurane: time-course of effect. *Anesthesia and Analgesia* 1991; **72**: 469–473.
10. Weber S, Brandom BW, Powers DM, Sarner JB, Woelfel SK, Cook DR, Foster VJ, McNulty BF, Weakly JN. Mivacurium chloride (BW B1090U)-induced neuromuscular blockade during nitrous oxide–isoflurane and nitrous oxide–narcotic anesthesia in adult surgical patients. *Anesthesia and Analgesia* 1988; **67**: 495–499.
11. Sarner JB, Brandom BW, Woelfel SK, Dong ML, Horn MC, Cook DR, McNulty BF, Foster VJ. Clinical pharmacology of mivacurium chloride (BW B1090U) in children during nitrous oxide–halothane and nitrous oxide–narcotic anesthesia. *Anesthesia and Analgesia* 1989; **68**: 116–121.
12. Goudsouzian NG, Alifimoff JK, Eberly C, Smeets R, Griswold J, Miler V, McNulty BF, Savarese JJ. Neuromuscular and cardiovascular effects of mivacurium in children. *Anesthesiology* 1989; **70**: 237–242.
13. Kalli I. Effect of surface electrode positioning on the compound action potential evoked by ulnar nerve stimulation in anaesthetized infants and children. *British Journal of Anaesthesia* 1989; **62**: 188–193.
14. Meretoja OA, Olkkola KT. Pharmacodynamics of mivacurium in children, using a computer-controlled infusion. *British Journal of Anaesthesia* 1993; **71**: 232–237.
15. Gregory GA, Eger EI II, Munson ES. The relationship between age and halothane requirements in man. *Anesthesiology* 1969; **30**: 488–491.
16. Cameron CB, Robinson S, Gregory GA. The minimum anesthetic concentration of isoflurane in children. *Anesthesia and Analgesia* 1984; **63**: 418–420.
17. Alifimoff JK, Goudsouzian NG. Continuous infusion of mivacurium in children. *British Journal of Anaesthesia* 1989; **63**: 520–524.
18. Brandom BW, Sarner JB, Woelfel SK, Dong ML, Horn MC, Borland LM, Cook DR, Foster VJ, McNulty BF, Weakly JN. Mivacurium infusion requirement in paediatric surgical patients during nitrous oxide–halothane and during nitrous oxide–narcotic anesthesia. *Anesthesia and Analgesia* 1990; **71**: 16–22.
19. Choi WW, Mehta MP, Murray DJ, Sokoll MD, Forbes RB, Gergis SD, Abou-Donia M, Kirchner J. Neuromuscular and cardiovascular effects of mivacurium chloride in surgical patients receiving nitrous oxide–narcotic or nitrous oxide–isoflurane anaesthesia. *Canadian Journal of Anaesthesia* 1989; **36**: 641–650.
20. Powers DM, Brandom BW, Cook DR, Byers R, Sarner JB, Simpson K, Weber S, Woelfel SK, Foster VJ. Mivacurium infusion during nitrous oxide–isoflurane anesthesia: A comparison with nitrous oxide–opioid anesthesia. *Journal of Clinical Anesthesia* 1992; **4**: 123–126.
21. Meretoja OA. Neuromuscular blocking agents in paediatric patients: influence of age on the response. *Anaesthesia and Intensive Care* 1990; **18**: 440–448.
22. Meretoja OA, Taivainen T. Recent developments in muscle relaxation in children. *Current Anaesthesia and Critical Care* 1994; **5**: 202–208.

British Journal of Anaesthesia 1996; **76**: 239–244

Edrophonium antagonism of intense mivacurium-induced neuromuscular block in children

M. ABDULATIF, A. AL-GHAMDI, M. AL-SANABARY AND M. E. ABDEL-GAFFAR

Summary

We have studied the time course of recovery after administration of edrophonium during intense mivacurium block in children aged 2–10 yr, using thumb acceleration in response to train-of-four (TOF) stimulation. Forty-three children receiving alfentanil, propofol, nitrous oxide, isoflurane anaesthesia and mivacurium 0.2 mg kg^{-1} were allocated randomly to one of three groups. Patients in group 1 ($n = 15$) received edrophonium 1 mg kg^{-1}, 2 min after maximum block (intense block group). At the time of administration of edrophonium in this group, there was no response to TOF stimulation (100% block) and the post-tetanic count was 10.7 (range 0–20). Patients in group 2 received the same dose of edrophonium after 10% recovery of the first twitch (T1) in the TOF (conventional reversal). Patients in group 3 ($n = 13$) recovered spontaneously. All patients developed complete suppression of twitch height in response to the bolus dose of mivacurium. All recovery times were measured from the point of maximum block after mivacurium. Mean time for 25% recovery of T1 (clinical duration) was 3.8 (SD 1.1) min in the intense block group. This was significantly shorter than the conventional reversal (8.3 (2.4) min) and spontaneous recovery (9.2 (3.5) min) groups ($P < 0.001$). The times for 75% and 90% recovery of T1 were shorter in the intense block group (9.4 (2.8), 12.3 (4.2) min) compared with the conventional (13.1 (3.8), 17.3 (4.8) min) and spontaneous recovery (14.9 (4.5), 17.9 (5.2) min) groups ($P < 0.01$). Total recovery time required for 70% recovery of the TOF ratio (T4/T1) was 8.8 (2.4) min in the intense block group. This was significantly shorter than the conventional reversal (11.9 (3.2) min) ($P < 0.05$) and spontaneous recovery (17.1 (4.0) min) groups ($P < 0.001$). Conventional reversal was associated with a shorter total recovery time compared with spontaneous recovery ($P < 0.01$). The recovery index (time interval between T1 25% and 75%) was comparable in groups 1–3 (5.5 (2.0), 4.8 (2.1) and 5.7 (1.4) min respectively). Ten minutes after development of maximum block, the numbers of patients who recovered adequately (TOF ratio 70% or more) were, respectively, 12 (80%), 8 (53%) and 1 (8%) in groups 1–3. We conclude that edrophonium antagonized intense (no response to TOF stimulation) mivacurium-induced block in children, with significant reduction in the recovery times of T1 and TOF ratio compared with conventional reversal and spontaneous recovery. (*Br. J. Anaesth.* 1996; **76**: 239–244)

Key words

Antagonists neuromuscular block, edrophonium. Neuromuscular block, mivacurium. Children.

Mivacurium, a short-acting, non-depolarizing neuromuscular blocking agent, has been studied in children to create dose–response curves and to maintain adequate neuromuscular block with a continuous infusion [1–4]. A common finding was that children have increased dose requirements and faster spontaneous recovery than adults under comparable conditions. Recent evidence also suggests that, compared with adults, children have different responses to antagonist-assisted recovery of mivacurium-induced block. When the reversal agents were given at a defined point of recovery, antagonism occurred more rapidly and the dose required to produce an equivalent effect was less in children than in adults [5].

Conventional antagonism of residual non-depolarizing neuromuscular block is usually attempted at the conclusion of surgery after detection of a variable degree of spontaneous recovery. In clinical practice, however, anaesthetic or surgical requirements for neuromuscular block can change suddenly, leaving the anaesthetist in the awkward situation of needing to reverse intense non-depolarizing block, for example failed tracheal intubation after a full paralysing dose of a non-depolarizing neuromuscular blocking agent. Several investigators have tried to antagonize intense non-depolarizing neuromuscular block in adults [6–8] and children [9]. At this depth of block, administration of neostigmine or edrophonium failed to shorten the total recovery time of atracurium- or vecuronium-induced block.

In a recent report [10], we demonstrated that in adults, edrophonium antagonized intense miva-

---

MOHAMED ABDULATIF*, MD, MOHGA AL-SANABARY, MD, Department of Anaesthesia, Cairo University, Egypt. ABDULMOHSIN AL-GHAMDI, MD, MOHAMED EMAD ABDEL-GAFFAR, MD, King Faisal University, Saudi Arabia. Accepted for publication: October 4, 1995.

*Address for correspondence: Anaesthesiology Department, King Fahad Hospital of the University, Al-Khobar 31952, PO Box 40081, Saudi Arabia.

curium block with a reduction in clinical duration. In the present study, we have examined the time course of recovery after early administration of edrophonium during intense (no response to train-of-four (TOF) stimulation) mivacurium-induced block in children.

Patients and methods

We studied 43 children, ASA I or II, aged 2–10 yr (mean 5.1 yr) and weighing 10–30 kg (mean 17.4 (SD 5.1) kg). All patients were undergoing low risk, short, elective ear and throat surgery, for example tonsillectomy, adenoidectomy or myringotomy. This study was approved by the Hospital Ethics Committee and all parents gave written informed consent. We excluded any patient suffering from cardiac, vascular, respiratory, hepatic, renal or neuromuscular disorders. Patients receiving medications known to affect the activity of plasma cholinesterase enzyme or normal neuromuscular transmission were also excluded.

All patients were premedicated with oral midazolam 0.5 mg kg^{-1} 20–30 min before surgery. In the operating room, an i.v. infusion of 5 % glucose in 0.225 % NaCl solution was given at a rate of 4–6 ml kg^{-1} h^{-1} through a peripheral arm vein. The ECG was monitored continuously and arterial pressure was measured every 5 min using an automatic oscillotonometer (Dinamap). Anaesthesia was induced in all patients with alfentanil 20 µg kg^{-1} and propofol 3–3.5 mg kg^{-1}, and maintained with 1 % inspired concentration of isoflurane and 70 % nitrous oxide in oxygen. Tracheal intubation was performed without the use of neuromuscular blocking agents. Ventilation was controlled to maintain normocapnia (end-tidal carbon dioxide partial pressure 4.6–5.3 kPa). The temperature of the skin overlying the adductor pollicis muscle was monitored and maintained at 32–33 °C. Concentrations of isoflurane, nitrous oxide, carbon dioxide and oxygen saturation were determined continuously by a multiple gas analyser (Capnomac Ultima-SVI, Datex Instrumentation Corporation, Helsinki, Finland).

The ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2 ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz repeated every 15 s. An acceleration piezoelectric transducer (Biometer International, Odense, Denmark) was fastened to the volar surface of the distal phalanx of the left thumb using adhesive tape. Free movement during evoked thumb adduction was ensured by fixation of the extended four ulnar fingers by an elastic bandage. Evoked left thumb acceleration, in response to ulnar nerve stimulation and adductor pollicis contractions, was measured using a TOF Guard neuromuscular monitor (Biometer International, Odense, Denmark).

After induction of anaesthesia, a period of 7–10 min was required to stabilize the twitch height recording in all patients. During this period, all patients received the same concentration of isoflurane (1 % inspired). After twitch stabilization, each patient received a single i.v. bolus dose of mivacurium 0.2 mg kg^{-1}. Patients were allocated randomly to one of three groups according to the mode of recovery and timing of antagonist administration. Patients in group 1 ($n = 15$) received edrophonium 1 mg kg^{-1}, 2 min after development of maximum block following mivacurium injection (intense block group). Patients in group 2 ($n = 15$) received the same dose of edrophonium when T1 recovered spontaneously to 10 % of its control value (conventional reversal group). Patients in group 3 ($n = 13$) recovered spontaneously. Atropine 10 µg kg^{-1} was given just before edrophonium to all patients in groups 1 and 2. In the intense block group, if there was no response to TOF stimulation at the time of edrophonium administration, deep block was assessed using post-tetanic stimulation applied to the contralateral ulnar nerve (right arm). The post-tetanic sequence comprised: 50 Hz tetanic stimulation for 5 s, pause 3 s, followed by 1 Hz single twitch stimulation for 20 s. After tetanic stimulation, the number of muscle contractions in response to 1-Hz single twitch stimulation was assessed visually and constituted the post-tetanic count (PTC). A similar current output was used for both hands. PTC was assessed in the contralateral hand to avoid the possible effects of tetanic stimulation on the course of neuromuscular recovery [11, 12].

All information derived from the acceleration transducer, including the duration of the period of no response to TOF stimulation (100 % block), was recorded on a memory card and the following variables were determined from the computer printout of the TOF Guard machine: (1) onset of mivacurium block: time interval between the end of injection of mivacurium and development of maximum block; (2) mivacurium antagonist time: time interval between development of maximum block and edrophonium administration; (3) PTC at the time of administration of edrophonium in the intense block group; (4) time between development of maximum block after mivacurium and recovery of T1 to 25 %, 75 % and 90 % of its control; (5) recovery index (RI): time required for recovery of T1 from 25 % to 75 % of its control; (6) total recovery time: time between development of maximum block after mivacurium and recovery of TOF ratio (T4/T1) to a value of 70 %; (7) T1 and TOF ratio every minute for at least 20 min after development of maximum block; and (8) number of patients in each group who were adequately recovered (TOF of 70 % or more) after 10 min from the development of maximum block after mivacurium.

All patients continued to receive 0.5–1 % isoflurane throughout the investigation. Antagonism was considered adequate at a TOF ratio of 70 %. After tracheal extubation, patients were kept in the recovery room for at least 1 h. Patients were assessed frequently for clinical signs of adequate recovery.

Statistical analyses were performed by one-way analysis of variance (ANOVA) and Student–Newman–Keuls test was used when multiple comparisons between different groups were required. Differences were considered significant at $P < 0.05$.

Table 1 Recovery characteristics (mean (SD)). Mivacurium antagonist time = time interval between maximum block after mivacurium and edrophonium administration; T1 (25), T1 (75) and T1 (90) = time interval between maximum block after mivacurium and recovery of the first twitch in the train of four (T1) to a value of 25%, 75% and 90% of its control; RI = recovery index: time interval between T1 25% and 75%; total recovery time = time interval between maximum block after mivacurium and a train-of-four ratio (T4/T1) of 70%. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with conventional reversal group; ††$P < 0.01$, †††$P < 0.001$ compared with spontaneous recovery group

Group	Mode of recovery	Mivacurium antagonist time (min)	T1 (25) (min)	T1 (75) (min)	T1 (90) (min)	RI (min)	Total recovery time (min)
1	Intense block, edrophonium after 2 min (*n* = 15)	2.0***	3.8 (1.1)***†††	9.4 (2.8)**††	12.3 (4.2)**††	5.5 (2.0)	8.8 (2.4)*†††
2	Conventional reversal, edrophonium at T1 (10%) (*n* = 15)	7.8 (2.6)	8.3 (2.4)	13.1 (3.8)	17.3 (4.8)	4.8 (2.1)	11.9 (3.2)††
3	Spontaneous recovery (*n* = 13)	—	9.2 (3.5)	14.9 (4.5)	17.9 (5.2)	5.7 (1.4)	17.1 (4.0)

Results

All patients developed complete ablation of the TOF response (100% block) after administration of the bolus dose of mivacurium. Onset time was comparable in all groups (mean 2.1 (range 1–3.3) min). At the time of antagonist administration, there was no response to TOF stimulation (100% block) in the intense block group with a mean PTC of 10.7 (0–20). Mivacurium antagonism time was significantly shorter in the intense block group compared with the conventional reversal group (table 1, fig. 1).

The times taken for T1 to reach 25%, 75% and 90% of control and for the TOF ratio to recover to 70% were significantly shorter in the intense block group compared with the conventional reversal and spontaneous recovery groups (table 1, figs 1–3). However, the rate of recovery of T1, reflected by the duration of the RI, was comparable in all groups and was not affected by the method of recovery or the timing of edrophonium administration (table 1, figs 1, 2). There was no difference in the times to recovery of T1 between the spontaneous recovery and conventional reversal groups. Total recovery time was shorter in the conventional reversal group compared with the spontaneous recovery group (table 1).

Ten minutes after the development of maximum block, the numbers of patients adequately recovered were 12 (80%), 8 (53%) and 1 (8%) in groups 1–3, respectively.

No patient manifested clinical signs of muscle weakness in the recovery room.

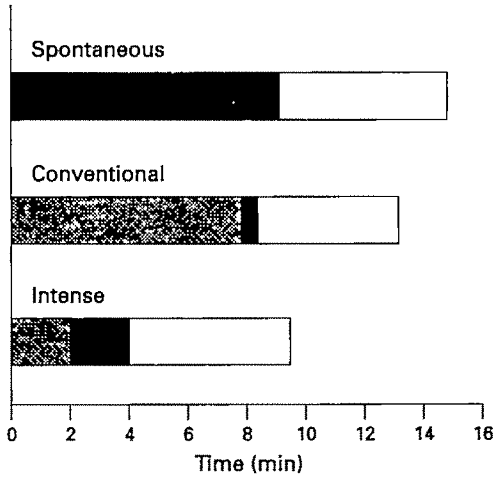


Figure 1 Mean times for recovery of the first twitch of the TOF (T1) after spontaneous or edrophonium-assisted recovery of two levels of mivacurium-induced block. Mivacurium antagonist time (▨) = interval between development of maximum block after mivacurium and edrophonium administration; clinical duration (■) = interval between development of maximum block after mivacurium and recovery of T1 to 25% of its control; recovery index (□) = interval between 25% and 75% recovery of T1. For the two groups of patients who were given edrophonium, the clinical duration includes the mivacurium antagonist time. For all groups, the time required for 75% recovery of T1 is the sum of clinical duration and recovery index.

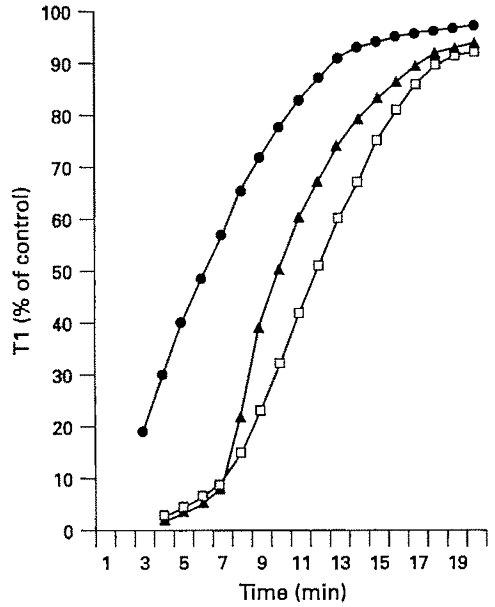


Figure 2 Mean time course and rate of recovery of the first twitch in the train of four (T1) after spontaneous (□) or edrophonium-assisted recovery of two levels of mivacurium-induced block (intense (●) and conventional (▲)). Time zero = when maximum block developed after bolus doses of mivacurium.

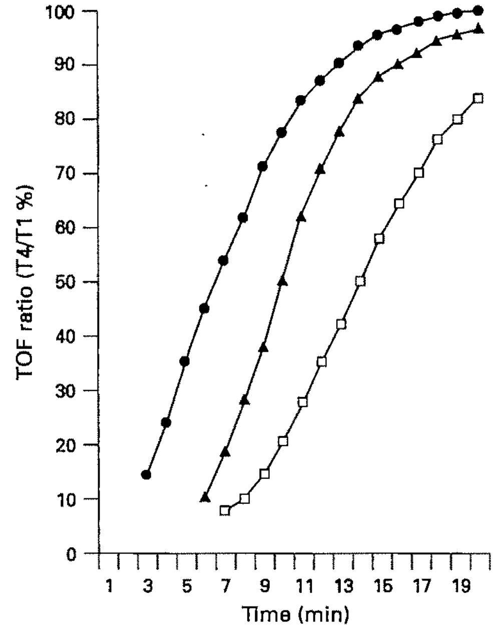


Figure 3 Mean time course and rate of recovery of the train-of-four (TOF) ratio after spontaneous (□) or edrophonium-assisted recovery of two levels of mivacurium-induced block (intense (●) and conventional (▲)). Time zero = when maximum block developed after bolus doses of mivacurium.

Discussion

Mivacurium is unique among non-depolarizing neuromuscular blockers in that it is metabolized by plasma cholinesterase [13]. The activity of butyrylcholinesterase is inhibited by neostigmine [14]. A recent study in children receiving mivacurium for neuromuscular block demonstrated that neostigmine decreased plasma cholinesterase activity by about 85 % but edrophonium had no effect [15]. Earlier reports suggested that spontaneous recovery from mivacurium-induced block may be preferable to the routine use of antagonists [13]. However, later studies showed that in adults, when evidence of spontaneous recovery was present at the end of surgery, antagonism of residual block by neostigmine or edrophonium was superior to spontaneous recovery [16, 17]. The time saved by conventional reversal of mivacurium-induced block in adults is in the range of 7–9 min [13, 16]. In children, when anticholinesterases were given at a twitch height equivalent to 25 % of control during recovery from mivacurium-induced block, the time saved by antagonist-assisted compared with spontaneous recovery of mivacurium block was short and clinically unimportant [15]. This was also the case with conventional reversal in the present study. Compared with spontaneous recovery, conventional reversal was not associated with any time saving with respect to T1 recovery. The difference between total recovery time in the conventional and spontaneous recovery groups was only 5 min. In contrast, edrophonium antagonism of intense mivacurium block was associated with significant reduction in the recovery times of T1 and total recovery time compared with spontaneous recovery. This time saving may be particularly beneficial in a busy day-care facility where the use of mivacurium may be especially indicated.

Our previous experience with antagonism of intense mivacurium block in adults demonstrated that edrophonium reduced the clinical duration but not the total recovery time to a TOF ratio of 70 % [10]. In contrast, in the present study early administration of edrophonium during intense mivacurium-induced block in children was associated with shorter times for T1 and TOF recovery. The times to 25 %, 75 % and 90 % recovery of T1 were reduced compared with conventional reversal and spontaneous recovery. Compared with the adult study, edrophonium antagonism of intense mivacurium block in children was also associated with reduction in total recovery time. Ten minutes after development of maximum block, most patients (80 %) who received edrophonium during intense mivacurium-induced block had recovered adequately (TOF ratio 70 % or more). A general observation was that most of the recovery times of T1 and the TOF ratio in the intense and conventional reversal groups were markedly shorter (50 % or less) in children compared with adults. Spontaneous recovery in children was also faster than antagonist-assisted conventional reversal in adults. The discrepancy between adults and children with respect to recovery after edrophonium antagonism of intense mivacurium block may be an age-related variation in the response to mivacurium, methodological differences, or both, between the two studies.

Spontaneous recovery from neuromuscular blocking drugs is more rapid in children aged 1–10 yr than in adults [18]. This is especially the case with neuromuscular blocking drugs that are largely metabolized in plasma, for example atracurium and mivacurium [19]. An inverse relationship was found between plasma cholinesterase activity and time to first response to TOF stimulation with the use of mivacurium [20–22]. Mean cholinesterase activity in children is about 30% above that in adults [23]. Therefore, faster recovery from the effects of mivacurium in children could be related to increased clearance secondary to changes in the function of its excretory pathways, including plasma esterases. It has been suggested also that the rapid rate of spontaneous recovery from mivacurium-induced block in children may be related to rapid redistribution from the biophase [19]. Beemar and co-workers [24] pointed out that reversal time is determined by two processes: direct antagonism by the anticholinesterase and spontaneous recovery from the effects of the neuromuscular blocking agent, with the latter becoming the major determinant at profound levels of block.

The main differences between the two studies were in the method of recording of the evoked adductor pollicis response and the depth of block at which antagonism was attempted in the intense block group. Force displacement and piezoelectric acceleration transducers were used in the adult and children studies, respectively. A good level of accuracy and correlation between the two types of transducers have been reported by several investigators [25–27]. Therefore, the differences in neuromuscular monitoring equipment do not seem to be sufficient to explain the marked discrepancy between the two age groups.

There was no response to TOF stimulation at the time of administration of edrophonium in the intense block groups in the adult and children studies. However, mean PTC recorded at the time of edrophonium administration in children was 10.7. Mean PTC recorded after the initial detection of post-tetanic response in adults was 3 [10]. This finding confirms the relative resistance of children to mivacurium-induced block and may partly explain the difference in recovery characteristics.

Mangat and co-workers [28] reported that in children aged 2–12 yr, receiving halothane anaesthesia, mean clinical duration of neuromuscular block was 3.2 (range 2.9–3.6) min and 10.25 (9–11.6) min during spontaneous recovery from intubating doses of suxamethonium 1 mg kg^{-1} and mivacurium 0.2 mg kg^{-1}, respectively. The clinical duration of mivacurium-induced block in the spontaneous recovery group in the present study was 9.2 (3.5) min and was comparable with that reported by Mangat and colleagues. However, with early administration of edrophonium during intense mivacurium-induced block, the clinical duration was reduced markedly (3.8 (1.1) min) to approach that of suxamethonium. This finding may be particularly beneficial if the indication for antagonism of intense block was failed tracheal intubation after a bolus dose of mivacurium. In this clinical situation, resumption of adequate breathing may be life saving. Mangat and co-workers [28] demonstrated that in children receiving mivacurium 0.2 mg kg^{-1} and monitored with the use of an acceleration transducer, there was obvious disparity between recovery of respiratory muscles and the adductor pollicis brevis muscle. Spontaneous ventilation was present when T1 had recovered to only 10% of control. This suggests that early antagonism of intense mivacurium-induced block in children can restore spontaneous breathing within 3–4 min after development of maximum block.

An alternative approach to accelerate recovery from intense mivacurium-induced block might be to administer human plasma cholinesterase in the form of either whole blood or a highly purified human plasma cholinesterase preparation. Experimental studies in anaesthetized cats have indicated that antagonism of intense mivacurium-induced block could be achieved with purified human plasma cholinesterase enzyme [29]. However, Bevan [30] pointed out that the use of plasma cholinesterase preparations to antagonize intense mivacurium-induced block in humans may be considered inappropriate as it may increase the risk of serious viral infections related to transfusion of blood products. The results of the present study also indicate that this approach is not only hazardous but unnecessary in children, as edrophonium can antagonize intense mivacurium block within a clinically acceptable recovery time.

References

1. Alifimoff KJ, Goudsouzian NG. Continuous infusion of mivacurium in children. *British Journal of Anaesthesia* 1989; **63**: 520–524.
2. Sarner JB, Brandom BW, Woelfel SK. Clinical pharmacology of mivacurium chloride (BWB 1090 U) in children during nitrous oxide–halothane and nitrous oxide–narcotic anesthesia. *Anesthesia and Analgesia* 1989; **68**: 116–121.
3. Goudsouzian NG, Alifimoff JK, Eberly C, Smeets R, Griswold J, Miler V, McNulty BF, Savarese JJ. Neuromuscular and cardiovascular effects of mivacurium in children. *Anesthesiology* 1989; **70**: 237–242.
4. Brandom BW, Sarner JB, Woelfel SK, Dong ML, Horn MC, Borland LM, Cook DR, Foster VJ, McNulty BF, Weakly JN. Mivacurium infusion requirement in pediatric surgical patients during nitrous oxide–halothane and during nitrous oxide–narcotic anesthesia. *Anesthesia and Analgesia* 1990; **71**: 16–22.
5. Bevan JC, Blackman LT, Kuahgi R, Reimer EJ, Smith MF, Stephenson CA, Tousignant C, Bevan DR. Neostigmine and edrophonium reversal of mivacurium neuromuscular blockade in adults and children. *Canadian Journal of Anaesthesia* 1995; **42**: A73.
6. Magorian TT, Lynam DP, Caldwell JE, Miller RD. Can early administration of neostigmine, in single or repeated doses, alter the course of neuromuscular recovery from a vecuronium-induced neuromuscular blockade? *Anesthesiology* 1990; **73**: 410–414.
7. Engbaek J, Ostergaard D, Skovgaard LT, Viby-Mogensen J. Reversal of intense neuromuscular blockade following infusions of atracurium. *Anesthesiology* 1990; **72**: 803–806.
8. Caldwell JE, Robertson EN, Baird WLM. Antagonism of profound neuromuscular blockade induced by vecuronium or atracurium: comparison of neostigmine and edrophonium. *British Journal of Anaesthesia* 1986; **58**: 1285–1289.
9. Gwinnutt CL, Walker RWM, Meakin G. Antagonism of intense atracurium-induced neuromuscular block in children. *British Journal of Anaesthesia* 1992; **67**: 13–16.
10. Abdulatif M. Recovery characteristics after early administration of anticholinesterases during intense mivacurium-induced neuromuscular block. *British Journal of Anaesthesia* 1995; **74**: 20–25.
11. Lee C, Katz RL. Neuromuscular pharmacology: a clinical update and commentary. *British Journal of Anaesthesia* 1980; **52**: 173–188.
12. Brull SJ, Connelly NR, O'Connor TZ, Silverman DG. Effect

of tetanus on subsequent neuromuscular monitoring in patients receiving vecuronium. *Anesthesiology* 1991; **74**: 64–70.

13. Savarese JJ, Ali HH, Basta SJ, Embree PB, Scott RPF, Sunder N, Weakly JN, Wastila WB, El-Sayad HA. The clinical neuromuscular pharmacology of mivacurium chloride (BW B 1090U): a short acting nondepolarizing ester neuromuscular blocking drug. *Anesthesiology* 1988; **68**: 723–732.
14. Baraka A, Wakid N, Mansour R, Haddad W. Effect of neostigmine and pyridostigmine on plasma cholinesterase activity. *British Journal of Anaesthesia* 1981; **53**: 849–852.
15. Fonseca J, Chaudry IA, Marin F, Halliday NJ, Radvany T, Bikhazi GB, Foldes FF. Mivacurium block: spontaneous and neostigmine or edrophonium induced recovery in children. *Anesthesia and Analgesia* 1994; **78**: S118.
16. Naguib M, Abdulatif M, Al-Ghamdi A, Hamo I, Nouheid R. Dose–response relationships for edrophonium and neostigmine antagonism of mivacurium-induced neuromuscular block. *British Journal of Anaesthesia* 1993; **71**: 709–714.
17. Curran MJ, Shaff L, Savarese JJ, Ali HH, Risner M. Comparison of spontaneous and neostigmine accelerated recovery from mivacurium neuromuscular blockade. *Anesthesiology* 1988; **69**: A528.
18. Bevan DR, Donati F, Kopman AF. Reversal of neuromuscular blockade. *Anesthesiology* 1992; **77**: 785–805.
19. Brandom BW. Neuromuscular blocking drugs. *Anesthesiology Clinics of North America* 1991; **9**: 781–800.
20. Stergaard D, Jensen FS, Jensen E, Skovgaard LT, Viby Mogensen J. Influence of plasma cholinesterase activity on recovery from mivacurium-induced neuromuscular blockade in phenotypically normal patients. *Acta Anaesthesiologica Scandinavica* 1992; **37**: 702–706.
21. Frampton JE, McTavish D. Mivacurium: a review of its pharmacology and therapeutic potential in general anaesthesia. *Drugs* 1993; **45**: 1066–1089.
22. Lien CA, Schmith VD, Embree PB, Belmont MR, Wargin WA, Savarese JJ. The pharmacokinetics and pharmacodynamics of the stereoisomers of mivacurium in patients receiving nitrous oxide–opioid–barbiturate anesthesia. *Anesthesiology* 1994; **80**: 1296–1302.
23. Whittaker M. Plasma cholinesterase variants and the anaesthetist. *Anaesthesia* 1980; **35**: 174–197.
24. Beemar GH, Bjorksten AR, Dawson PJ, Dawson RJ, Heenan PJ, Robertson BA. Determinants of the reversal time of competitive neuromuscular block by anticholinesterases. *British Journal of Anaesthesia* 1991; **66**: 469–475.
25. Viby-Mogensen J, Jensen E, Werner M, Kirkegaard HN. Measurement of acceleration: a new method of monitoring neuromuscular function. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 45–48.
26. May O, Kirkegaard HN, Werner MU. The acceleration transducer: an assessment of its precision in comparison with a force displacement transducer. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 239–243.
27. Itagaki T, Tai K, Katshumata N, Suzuki H. Comparison between a new acceleration transducer and a conventional force transducer in the evaluation of twitch response. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 347–349.
28. Mangat PS, Evans DE, Harmer M, Lunn JN. A comparison between mivacurium and suxamethonium in children. *Anaesthesia* 1993; **48**: 866–869.
29. Bownes PB, Hartman GS, Chiscolm BS, Savarese JJ. Antagonism of mivacurium blockade by purified human butyryl cholinesterase in cats. *Anesthesiology* 1992; **77**: A909.
30. Bevan DR. Prolonged mivacurium-induced neuromuscular block. *Anesthesia and Analgesia* 1993; **77**: 4–6.

British Journal of Anaesthesia 1996; **76**: 245–250

Fuzzy logic control of inspired isoflurane and oxygen concentrations using minimal flow anaesthesia

M. CURATOLO, M. DERIGHETTI, S. PETERSEN-FELIX, P. FEIGENWINTER, M. FISCHER AND A. M. ZBINDEN

Summary

In order to evaluate the performance of feedback fuzzy logic control of inspired oxygen and isoflurane concentrations, we studied 30 patients undergoing discectomy for lumbar ($n = 26$) or cervical ($n = 4$) disc herniation. Patients were allocated random to one of two groups: a standard group ($n = 15$) with low flow anaesthesia (1.2–1.3 litre min^{-1}) and manual control of gas concentrations; and a fuzzy group ($n = 15$) with minimal flow (0.5 litre min^{-1}) and fuzzy logic feedback control of gas concentrations. Fuzzy logic control achieved and maintained very accurately the desired isoflurane concentration. Oxygen concentration was controlled more precisely than in the standard group. Delivery and costs of oxygen and nitrous oxide were significantly lower in the fuzzy group ($P < 0.01$). Accumulation of foreign gases was observed in one patient during low flow and in 11 patients during minimal flow anaesthesia. In conclusion, fuzzy logic control of inspired oxygen and isoflurane concentration during minimal flow anaesthesia was reliable and reduced anaesthetic gas delivery and costs. (*Br. J. Anaesth.* 1996; **76**: 245–250)

Key words

Anaesthetic techniques, low flow. Anaesthetics volatile, isoflurane. Computers. Model, computer simulation.

General anaesthesia is usually performed by delivering a fresh gas flow of 1.5–6 litre min^{-1}. As flow is increased, increasing amounts of anaesthetic gases are lost through the escape valve [1]. This increases costs [2] and results in a potential health hazard to personnel [3, 4] and destruction of the ozone layer [5]. Furthermore, a high fresh gas flow results in cold and dry inspired gases that may damage the tracheal epithelium [6].

Closed-circuit anaesthesia minimizes these untoward effects, but cannot be undertaken with many circle systems, mainly because of the high leakage rate, the presence of a hanging bellow which may cause negative pressures in the system and inaccuracy of flowmeters. These restrictions apply to a lesser extent to minimal flow anaesthesia, in which a fresh gas flow of 0.5 litre min^{-1} is delivered. Leakage rates of less than 50 ml min^{-1} can usually be tolerated. Therefore, unlike closed-circuit, minimal flow anaesthesia can be performed with many of the circle systems available. Moreover, it is not necessary to continuously adjust oxygen delivery to maintain the volume of the system.

However, when using this technique, the inspired gas concentrations do not correspond with those in the fresh gas because of mixing with exhaled alveolar gases.

The aim of this study was to evaluate the use of feedback control of inspired oxygen and isoflurane concentration during minimal flow anaesthesia performed by anaesthetists not trained in the minimal flow technique. The system was based on fuzzy logic [7, 8]. In order to compare the performance of the feedback system with a widely used anaesthetic technique, a group of patients undergoing low flow anaesthesia (1.2–1.3 litre min^{-1}) with manual control of inspired oxygen and isoflurane concentrations was also studied.

Patients and methods

We studied 30 ASA I–II patients, undergoing microsurgical fenestration and discectomy for lumbar disc herniation ($n = 26$) or cervical microdiscectomy with interbody fusion ($n = 4$). Patients with coronary artery disease and diabetes mellitus were excluded. The study was approved by the local Ethics Committee and written informed consent was obtained from all patients.

Two groups were studied. In the standard group, anaesthesia comprised the routine method of our department, that is a fresh gas flow of 1.2–1.3 litre min^{-1} and manual control of inspired oxygen and isoflurane concentrations. In the fuzzy group, minimal flow anaesthesia (0.5 litre min^{-1}) was undertaken with fuzzy logic feedback control of inspired oxygen and isoflurane concentrations. The anaesthetist set the desired inspired oxygen and isoflurane

---

M. CURATOLO, MD, DEAA, S. PETERSEN-FELIX, MD, DEAA, P. FEIGENWINTER, M. FISCHER, MD, A. M. ZBINDEN, MD, PHD, Institute of Anaesthesiology and Intensive Care, Section of Research, University of Bern, Inselspital, 3010 Bern, Switzerland. M. DERIGHETTI, Automatic Control Laboratory, Swiss Federal Institute of Technology, Zürich, Switzerland. Accepted for publication: September 5, 1995.

Correspondence to M.C.

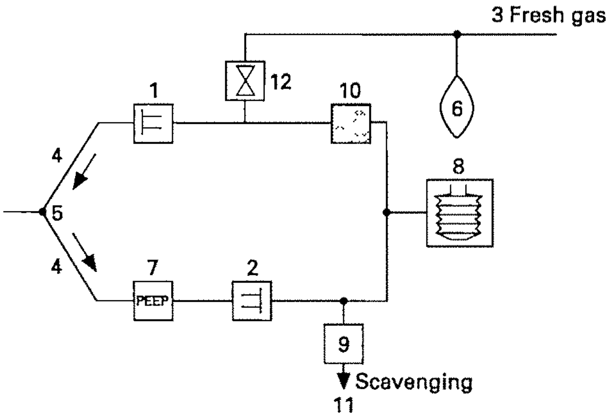


Figure 1 Simplified diagram of the anaesthetic system (Dräger Cicero IPPL). 1 = Inspiratory valve; 2 = expiratory valve; 3 = fresh gas inlet port; 4 = breathing tube; 5 = Y-piece; 6 = reservoir bag; 7 = PEEP valve; 8 = ventilator; 9 = overflow valve; 10 = carbon dioxide absorber; 11 = scavenging port; 12 = valve.

concentrations and the control system adjusted oxygen and isoflurane delivery to achieve and maintain the desired concentrations. The principles of fuzzy logic control are described in the appendix.

Patients were allocated randomly to each of the two groups on an alternate basis. They were premedicated with midazolam 7.5 mg orally, 30 min before induction of anaesthesia. Ringer's lactate 4 ml kg^{-1} was infused rapidly before induction of anaesthesia, followed by 2 ml kg^{-1} h^{-1} before surgery, 4 ml kg^{-1} h^{-1} during surgery and 2 ml kg^{-1} h^{-1} after skin closure. Anaesthesia was performed by staff members, residents or nurse anaesthetists with at least 1 yr experience in anaesthesia; they were not involved in the study but an anaesthetist involved in the study was always present.

After 3 min preoxygenation with 8 litre min^{-1} of 100 vol% oxygen via a face mask, anaesthesia was induced with fentanyl 1 μg kg^{-1} i.v. and thiopentone 5–7 mg kg^{-1}. The trachea was intubated after administration of vecuronium 0.1 mg kg^{-1}. After intubation, 30 vol% inspired oxygen and nitrous oxide, and isoflurane were delivered. The isoflurane concentration was set by the anaesthetist or nurse anaesthetist responsible for anaesthesia, without any influence from the anaesthetist involved in the study, to maintain systolic arterial pressure at 90–140 mm Hg. Vecuronium 1–2 mg was administered to maintain 0–2 responses to train-of-four stimulation of the ulnar nerve, evaluated visually. No other drug was administered until extubation.

After intubation, fresh gas flow was set to 4 litre min^{-1} for 15 min. Flow was then reduced to 1.2–1.3 litre min^{-1} in the standard group and 0.5 litre min^{-1} in the fuzzy group. To prevent accumulation of non-anaesthetic gases, when the cumulative inspired concentration of oxygen, nitrous oxide and isoflurane was lower than 85 vol%, fresh gas flow was increased manually to 10 litre min^{-1} until a total concentration of 97 vol% was achieved. After skin closure, flow was increased to 6 litre min^{-1} in both groups. Residual neuromuscular block was antagonized with neostigmine 2.5 mg i.v. and glycopyrronium 0.5 mg i.v. When four equal responses to train-of-four stimulation were observed, nitrous oxide was discontinued and 100% oxygen was administered. The trachea was extubated as soon as the patient opened the eyes to verbal command.

The period of the study was divided into three parts: induction, from the beginning of preoxygenation to the end of high flow anaesthesia; maintenance, from the beginning of low–minimal flow anaesthesia to the end of surgery; recovery, from the end of surgery to extubation.

We used the Cicero workplace anaesthesia machine (Drägerwerke AG, Germany) (fig. 1). This allows monitoring of ECG, non-invasive arterial pressure (measured every 2.5 min), haemoglobin oxygen saturation using pulse oximetry, and inspired and end-tidal concentrations of oxygen, nitrous oxide and isoflurane sampled at the mouthpiece of the tracheal tube. For safety reasons the same gases were sampled at the mouthpiece of the tracheal tube with an additional monitor (Hewlett Packard M 1025B, Andover, USA). Gas sampled for analysis was returned by connecting the outlet port of both monitors with the expiratory limb of the breathing system.

In the fuzzy group, the anaesthetist or nurse responsible for anaesthesia set fresh gas flow, isoflurane and oxygen concentrations using three dialling buttons on an analogue control panel. The target for inspired oxygen concentration was 30 vol%. The values of inspired concentrations of oxygen and isoflurane set in the control panel represented the desired concentrations, that is the information that the anaesthetist fed into the fuzzy system, which in turn set the flowmeter and vaporizer to achieve and maintain the desired concentrations. The fuzzy logic system controlled a Dräger 19.3 vaporizer driven by an external servo-motor. The servo-motor itself was driven by a PID-controlled amplifier, which in turn was controlled by an electronic interface. The vaporizer driver was built in our laboratory and had been used in a previous investigation [9]. It has an immediate response time without overshooting. The vaporizer and PID control system had been calibrated by gas chromatography. The relation between setting and output was linear with flows of 0.5–5 litre min^{-1}. For safety reasons, the isoflurane concentration in the fresh gas was measured using a Hoyer PAAM gas analyser (Hoyer, Bremen, Germany). Two mass flow controllers (Bronkhorst Hi-Tec, Ruurlo, the Netherlands) were used to supply a precise flow of nitrous oxide and oxygen. They can deliver gas flows from 0.24 to 12 litre min^{-1} with an error of ±0.2% of maximum flow and ±1% of actual flow. Lower gas flows were obtained by intermittently switching off the flows. The Cicero vaporizer and flowmeters were bypassed. Whenever the anaesthetist desired a rapid change of inspired gas concentrations, a "turbo-mode" could be activated. This resulted in a temporary increase in fresh gas flow to 10 litre min^{-1} until the desired concentration was achieved. Whenever the inspired oxygen concentration was less than 26 vol%, the control system temporarily increased the oxygen fresh gas flow to 4 litre min^{-1} until the inspired oxygen concentration reached 26 vol%.

We used two separate static logic fuzzy controllers for oxygen and isoflurane. Both had fixed rules and a cycle time of 10 s. The fuzzy logic controller of inspired oxygen concentration determined the variables of a PID controller. The inputs were the error between desired and measured value, and fresh gas flow. That for inspired isoflurane concentration had three inputs: error between desired and measured values, its integral and fresh gas flow.

In the standard group the anaesthetist or nurse changed the fresh gas flow, and isoflurane and oxygen concentrations using the control panel. The mass flow controllers and vaporizer described above were used. The set values of isoflurane and oxygen concentrations, however, represented the fresh gas concentration as during a normal anaesthetic procedure, the only difference being that the anaesthetist used the panel instead of the vaporizer and flowmeters directly. The target for inspired oxygen concentration during the maintenance period was 30 vol%. In the standard group the "turbo-mode" and the automatic increase in fresh gas flow, when the inspired oxygen concentration was lower than 26 vol%, were not available.

Desired and measured inspired concentrations of oxygen and isoflurane, fresh gas flows, fresh gas concentration of isoflurane and arterial pressure were sampled using the Cicero every 10 s and stored on a IBM compatible computer. The resolution of the measurement of isoflurane concentration was 0.1 vol%.

DATA ANALYSIS

Control of inspired oxygen concentration in the two groups was compared by computing the duration of episodes during which oxygen concentration was between 28 and 32 vol%.

The ability of the fuzzy control to achieve rapidly the desired isoflurane concentration is described as the time needed to change the isoflurane concentration, calculated as follows: time from change of isoflurane concentration to achievement of desired concentration, divided by the difference between previous and desired inspired concentration. Changes of 0.1 vol% were not analysed. Increasing and decreasing concentration of isoflurane were calculated separately. Overshoot was analysed by averaging the maximum difference between measured and desired isoflurane concentration observed during the first 2 min after achieving the desired concentration. The ability of fuzzy logic to maintain the desired isoflurane concentration was described by the frequency distribution of the deviation *(measured − desired) isoflurane concentration,* beginning 2 min after achieving the desired concentration, until the concentration was changed again.

Fresh gas delivery of oxygen and nitrous oxide was recorded using the set point signals of the mass flow controllers, and expressed as the mean of all values of fresh gas flow during each phase (induction, maintenance and recovery) in each patient. Isoflurane delivery was computed by calculating the mean of the product (total fresh gas flow × fresh gas concentration of isoflurane) during each phase in each patient. The fresh gas concentration of isoflurane represented the fraction of gas set at the vaporizer (e.g. 2 vol% = 0.02). Costs of oxygen, nitrous oxide and isoflurane were calculated by multiplying the delivery by the price of each agent.

The stability of anaesthesia was evaluated by computing the duration of episodes during which systolic arterial pressure was between 90 and 140 mm Hg.

Numerical variables in the two groups were compared by Student's t-test when data were distributed normally, otherwise the Mann–Whitney U test was used. Normality was checked by the Wilk–Shapiro test [10]. Categorical variables were analysed by Fisher's exact test. $P < 0.05$ was considered significant. The statistical package used was RS/1, version 4.3.3 (Bolt Beranek and Newman Inc., Cambridge, MA, USA).

Results

Patient characteristics, and duration of surgery and recovery phase are presented in table 1.

During maintenance, the inspired oxygen concentration remained at 28–32 vol% for a longer period in the fuzzy than in the standard group (table 2). In one patient in the fuzzy group and in five in the standard group, the inspired oxygen concentration reached a value of 26 vol%, once in each patient. The minimal value was 24 vol%, which occurred once in both groups. No particular event (e.g. disconnection, airways obstruction, etc.) preceded these decreases in the inspired oxygen concentration. When the critical value of 26 vol% was reached in the fuzzy group, the inspired oxygen concentration was increased automatically by the control system by increasing the oxygen fresh gas flow to 4 litre min^{-1}.

The performance of fuzzy logic control of inspired isoflurane concentration is described in table 3. Inspired isoflurane concentration was changed 125 times during the maintenance period. In 13 instances (nine patients) the desired concentration was achieved by activating the "turbo-mode", in nine instances isoflurane concentration was changed by 0.1% and in 52 the set point was changed again before the desired concentration had been achieved. In eight instances in which the desired concentration was reached, the set point had been increased (decreased) while isoflurane concentration was still decreasing (increasing), and before the previous desired concentration had been achieved. All of these 82 changes in isoflurane concentrations were not analysed. Thus, 26 increases and 17 decreases in inspired isoflurane concentration are shown in table 3. The ability of the system to maintain isoflurane concentration was expressed by the frequency distribution of the deviation (measured − desired) isoflurane concentration, measured 2 min after achieving the desired concentration, until the concentration was changed again. This phase lasted 30 s or less in seven instances, which were therefore excluded from analysis. Thus the ability of the system to maintain isoflurane concentration was analysed in 36 instances (table 3).

Table 1 Patient characteristics, and duration of surgery and recovery phase (median (25–75 percentiles))

	Standard group	Fuzzy group	*P*
Sex (M/F)	7/8	8/7	ns
Age (yr)	41 (35–51)	43 (37–49)	ns
Weight (kg)	72 (60–77)	77 (67–86)	ns
Preop. systolic arterial pressure (mm Hg)	120 (110–130)	130 (120–140)	< 0.05
Duration of surgery (min)	75 (58–109)	85 (52–117)	ns
Recovery phase (min)	17 (14–24)	16 (13–22)	ns

Table 2 Control of inspired oxygen (O_2) concentration in the two groups during the maintenance phase. The duration of episodes during which the concentration was between 28 and 32 vol%, below 28 and above 32 vol% are expressed as percentage of duration of the maintenance period. Median (25–75 percentiles) values are presented

	Standard group	Fuzzy group	*P*
O_2 concn 28–32 vol% (% of duration of period)	64% (47–94%)	82% (76–91%)	< 0.01
O_2 concn < 28 vol% (% of duration of period)	2% (0–10%)	1% (0–4%)	ns
O_2 concn > 32 vol% (% of duration of period)	23% (5–42%)	17% (9–20%)	< 0.05

Table 4 Stability of anaesthesia in the two groups during the maintenance period, evaluated by stability of systolic arterial pressure (SAP). The duration of episodes during which SAP was between 90 and 140 mm Hg, less than 90 and greater than 140 mm Hg are expressed as percentage of duration of the maintenance period. Median (25–75 percentiles) values are shown. No statistically significant difference between the two groups

	Standard group	Fuzzy group
SAP 90–140 mm Hg (% of duration of period)	97% (91–100%)	96% (91–100%)
SAP < 90 mm Hg (% of duration of period)	0% (0–0%)	0% (0–0%)
SAP > 140 mm Hg (% of duration of period)	1% (0–7%)	2% (0–9%)

The duration of episodes during which systolic arterial pressure was less than 90 or greater than 140 mm Hg is presented in table 4. Table 5 shows the inspired concentrations, delivery and costs of gases.

In four patients in the fuzzy group, 4–29 min after the beginning of minimal flow, low volume of gas in the circuit was detected by the alarm system. The volume was restored by briefly pressing the oxygen flush button. Median body weight of these patients was higher than that of the other 11 patients (87.5 and 73 kg, range 65–100 and 61–90, respectively), but the difference was not statistically significant.

In 11 patients in the fuzzy group and in one in the standard group, fresh gas flow had to be set at 10 litre min^{-1} for 45–60 s, because of high concentration of non-anaesthetic gases. This occurred in the fuzzy group for the first time 18–41 min after the beginning of minimal flow (median 22 min) and a total of 1–5 times in different patients. Within the fuzzy group, median body weight of the 11 patients who required high flow was higher than that of the other four patients (79 and 70 kg, range 62–100 and 61–77, respectively), but the difference was not statistically significant.

Discussion

We have assessed the performance of fuzzy logic control of inspired oxygen and isoflurane concentrations during minimal flow anaesthesia. As only the research anaesthetists involved in the study (and not those performing clinical anaesthesia) were familiar with the minimal flow technique, we could not study a control group of patients undergoing minimal flow anaesthesia with manual control of

Table 3 Description of the performance of fuzzy logic feedback control of inspired isoflurane concentration during the phase of minimal flow. n = Number of increases (n_1) and decreases (n_2) of isoflurane concentrations and of phases during which isoflurane concentration was not changed (n_3), which were included in the analysis. The first two variables describe the ability of the feedback system to achieve the desired isoflurane concentration, whereas the last one describes the ability to maintain the desired concentration, beginning 2 min after achieving the desired concentration, until the concentration was changed again. The 13 occasions when the "turbo-mode" was manually activated are not included. Median (25–75 percentiles) values are presented

Time to increase inspired isoflurane concn (s vol%$^{-1}$) ($n_1 = 26$)		700 (540–850)
Overshoot after increasing isoflurane concn (vol%) ($n_1 = 26$)		0.1 (0.1–0.2)
Time to decrease inspired isoflurane concn (s vol%$^{-1}$) ($n_2 = 17$)		660 (360–1130)
Overshoot after decreasing isoflurane concn (vol%) ($n_2 = 17$)		0.1 (0.1–0.2)
Frequency distribution of the deviation (measured – desired) isoflurane concentration when isoflurane concentration was not changed ($n_3 = 36$)	$\leqslant -0.3$ vol%	0%
	-0.2 vol%	3%
	± 0.1 vol%	94%
	$+0.2$ vol%	3%
	$\geqslant 0.3$ vol%	0%

Table 5 Median (25–75 percentiles) values of inspired concentration, delivery and costs of inhaled agents in the two groups during the maintenance period. Inspired concentrations were recorded every 10 s, and the values shown represent medians and 25–75 percentiles of the mean values calculated for each patient

	Standard group	Fuzzy group	*P*
Inspired concentration			
Oxygen (vol%)	30 (29–31)	30 (30–31)	ns
Isoflurane (vol%)	0.9 (0.8–1.2)	0.9 (0.7–1.1)	ns
Delivery			
Oxygen (litre min^{-1})	0.59 (0.52–0.64)	0.34 (0.31–0.40)	< 0.01
Nitrous oxide (litre min^{-})	0.94 (0.80–1.07)	0.32 (0.25–0.39)	< 0.01
Isoflurane (ml gas min^{-1})	18.2 (13.3–25.7)	16.2 (9.4–18.5)	ns
Costs			
Oxygen (Swiss Francs h^{-1})	0.05 (0.05–0.06)	0.03 (0.03–0.04)	< 0.01
Nitrous oxide (Swiss Francs h^{-1})	1.02 (0.86–1.15)	0.35 (0.27–0.42)	< 0.01
Isoflurane (Swiss Francs h^{-1})	6.40 (4.67–9.04)	5.68 (3.30–6.49)	ns
Total (Swiss Francs h^{-1})	7.36 (5.59–10.17)	6.02 (3.65–6.98)	< 0.05

inspired gas concentrations. However, although the standard group does not represent a true control group because of the different fresh gas flow used, it allows comparison of fuzzy controlled anaesthesia with a widely used anaesthetic technique. However, control of inspired oxygen and isoflurane concentrations is easier during low flow than during minimal flow anaesthesia and therefore, the experimental design was biased *against* the fuzzy logic system.

One may wonder why we developed a system controlling inspired isoflurane concentration, as most anaesthetists think in terms of end-tidal concentration and previous studies have shown good control of end-tidal concentration with other feedback algorithms [11, 12]. One reason is that end-tidal feedback control may not be feasible or reliable in some situations, such as during spontaneous ventilation or anaesthesia in children with a face mask. Furthermore, unlike the aforementioned studies [11], we used minimal flow anaesthesia, and the desired concentration was not fixed during operation [12] but changed according to anaesthetic requirements. During minimal flow anaesthesia there is usually a large difference between end-tidal and fresh gas concentrations and the response of end-tidal concentration to changes in the fresh gas concentration is very slow. Because of these features it is difficult to develop an automatic system controlling end-tidal concentration by directly adjusting fresh gas concentration. We therefore developed a system to control inspired concentration, which can be used later in the control of end-tidal concentration in a cascade feedback system.

The control of inspired oxygen concentration in the fuzzy group was more precise than in the standard group, in spite of the lower fresh gas flow delivered (table 2).

Fuzzy logic control achieved and maintained the desired inspired concentration of isoflurane during minimal flow anaesthesia very accurately: overshoot was not observed and the desired concentration (±0.1 vol%) was maintained for 94% of the time (table 3). The long time needed to achieve the desired concentration (table 3, which does not include the occasions when the "turbo-mode" was activated) was the result of the very low fresh gas flow delivered. The anaesthesia machine, Physioflex (Physio BV, Hoofddrops, The Netherlands), allows feedback control of gas concentrations during closed-circuit anaesthesia. The presence of a turbine hastens gas mixing. This allows rapid achievement of inspired concentration when the fresh gas concentration is changed, thereby facilitating development of a feedback system. Such a technical feature is not available in conventional anaesthetic systems, such as that used in our study.

It was not possible to compare the two groups in terms of control of inspired isoflurane concentration, as in the standard group the anaesthetist controlled the fresh gas concentration and was not requested to specify a desired inspired concentration. This was avoided because the anaesthetists were used to adjusting the vaporizer to reach a desired end-tidal concentration or a pharmacological effect, but not a specific inspired concentration.

During minimal flow anaesthesia a decrease in the volume of gas in the anaesthetic system was observed in four patients, probably because of persisting nitrous oxide uptake of the patient. Accumulation of foreign gases in the circuit, a well-known disadvantage of closed-circuit anaesthesia [13], occurred frequently. Accumulation of nitrogen causes dilution of oxygen and anaesthetic agents. High blood concentrations of acetone after long-term closed-circuit anaesthesia increase the incidence of postoperative nausea and vomiting [14]. Methane accumulation can disturb infrared analysis of volatile anaesthetics [15]. Frequent flushing of the system with high fresh gas flows to remove foreign gases partially offsets the advantages of the minimal flow technique. Flushing of the anaesthesia circuit rapidly removes nitrogen and methane from the system [13], but does not decrease blood concentrations of acetone during long-term closed-circuit anaesthesia [14]. At present it is not known if blood concentrations of acetone increase during minimal flow anaesthesia.

Unlike oxygen and nitrous oxide delivery, isoflurane delivery in the fuzzy group was not significantly lower than in the standard group ($P = 0.06$). This was in part the result of frequently flushing the system with high flows because of accumulation of foreign gases. This factor would have had a lower impact if we had studied longer operations, as nitrogen elimination from the body decreases with time. Furthermore, as a result of different individual requirements, inspired isoflurane concentration and delivery varied greatly (table 5). Therefore, the expected small difference in isoflurane delivery between low flow and minimal flow anaesthesia might only be detected by studying a large patient population.

Appendix

INTRODUCTION TO FUZZY LOGIC CONTROL

Fuzzy logic

By *crisp objects* we imply that something is of a yes-or-no-type rather than a more-or-less-type. For instance, in a set of individuals we may say "John is a boy". But if we wish to define body height and decide that a person of 170 cm or more is tall and the rest are short, we have to classify Peter, who is 169.9 cm, as "short", and John, who at 170 cm is only 1 mm taller, as "tall". In order to avoid this dilemma fuzzy logic is introduced, that is the boundaries of a set are *fuzzy* instead of *crisp*. This makes it possible to classify an element as being *to a certain degree* a member of a set, by introducing membership function values between 0 and 1 [16]. It should be noted that fuzzy sets and continuous membership functions are closer to human thinking.

Fuzzy logic and probability theory are different. Probability theory deals with questions such as: "there are 30 white balls and 70 black balls in a bag. I draw a ball without looking. Is this ball black?" Answer: "with a 70% probability it is." Fuzzy logic deals with questions such as: "I have a grey ball. Is this ball black?" Answer: "we assign the value 0 for absolute white and 1 for absolute black. The statement "the ball is black" has a truth value of, say, 0.2 (the ball is light grey)". Thus fuzziness does not imply randomness [17].

Knowledge-based control

The classical controller calculates the input signal of the plant to be controlled based on the difference between a reference signal and the actual output of the plant. For instance, a so-called PID controller considers the error, its integral and its range of change in computing the input signal for the "plant" according to a mathematical formula. It is also possible to design a controller which uses a knowledge base to perform the controller function. For instance, it is possible to control the speed of a car so that it is constant with the following set of rules:

IF (speed is very low) THEN (accelerate sharply)
IF (speed is low) THEN (accelerate slightly)
IF (speed is high) THEN (decelerate)
IF (speed is very high) THEN (brake)
IF (speed is low AND road is uphill) THEN (accelerate sharply)

The values for "very low", "low", etc., have to be defined crisply.

Fuzzy control

A fuzzy controller is a knowledge-based controller where the variables have fuzzy instead of crisp values. It consists of: a *fuzzification module* which performs linguistic classification of variables; a *fuzzy knowledge-base* similar to a regular knowledge-base as in the car example containing rules of the type IF (error is slightly negative) THEN (fresh gas concentration is small); an *inference engine* which uses the fuzzy rules in the knowledge-base to produce a fuzzy control output based on control inputs; and a *defuzzification module* which determines a crisp control value from a fuzzy control value.

Acknowledgement

We thank Pasquale Scaramozzino, PhD, lecturer in the Department of Economics at SOAS University of London, UK, for his comments on the statistical methods.

References

1. Zbinden AM, Feigenwinter P, Hutmacher M. Fresh gas utilization of eight circle systems. *British Journal of Anaesthesia* 1991; **67**: 492–499.
2. Bengtson JP, Sonader H, Stenqvist O. Comparison of costs of different anaesthetic techniques. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 33–35.
3. Spence AA. Environmental pollution by inhalation anaesthetics. *British Journal of Anaesthesia* 1987; **59**: 96–103.
4. Imberti R, Preseglio I, Imbriani M, Ghittori S, Cimino F, Mapelli A. Low flow anaesthesia reduces occupational exposure to inhalation anaesthetics. *Acta Anaesthesiologica Scandinavica* 1995; **39**: 586–591.
5. Dale O. Inhalation anaesthetics and the global environment. *Acta Anaesthesiologica Scandinavica* 1991; 35 (Suppl 96): 40–41.
6. Chalon J, Loew DAY, Malebranche J. Effects of dry anesthetic gases on tracheobronchial ciliated epithelium. *Anesthesiology* 1972; **37**: 338–343.
7. Martin JF. Fuzzy control in anesthesia. *Journal of Clinical Monitoring* 1994; **10**: 77–80.
8. Asbury AJ, Tzabar Y. Fuzzy logic: new ways of thinking for anaesthesia. *British Journal of Anaesthesia* 1995; **75**: 1–2.
9. Zbinden AM, Feigenwinter P, Petersen-Felix S, Hacisalihzade S. Arterial pressure control with isoflurane using fuzzy logic. *British Journal of Anaesthesia* 1995; **74**: 66–72.
10. Shapiro SS, Wilk MB. An analysis of variance test for normality (complete samples). *Biometrika* 1965; **52**: 591–611.
11. Morris P, Tatnall ML, Montgomery FJ. Controlled anaesthesia: a clinical evaluation of an approach using patient characteristics identified during uptake. *British Journal of Anaesthesia* 1983; **55**: 1065–1075.
12. Ross JAS, Wloch RT, White DC, Hawes DW. Servo-controlled closed-circuit anaesthesia. A method for the automatic control of anaesthesia produced by a volatile agent in oxygen. *British Journal of Anaesthesia* 1983; **55**: 1053–1060.
13. Morita S, Latta W, Hambro K, Snider MT. Accumulation of methane, acetone, and nitrogen in the inspired gas during closed-circuit anesthesia. *Anesthesia and Analgesia* 1985; **64**: 343–347.
14. Strauss JM, Hausdörfer J. Accumulation of acetone in blood during long-term anaesthesia with closed systems. *British Journal of Anaesthesia* 1993; **70**: 363–364.
15. Rolly G, Versichelen LF, Mortier E. Methane accumulation during closed-circuit anesthesia. *Anesthesia and Analgesia* 1994; **79**: 545–547.
16. Zadeh LA. Fuzzysets. *Information and Control* 1965; **8**: 338–352.
17. Bezdek JC. Fuzzy models—what are they and why? *IEEE Transactions on Fuzzy Systems* 1993; **1**: 1–6.

British Journal of Anaesthesia 1996; **76**: 251–257

LABORATORY INVESTIGATIONS

Methylprednisolone inhibits endotoxin-induced depression of contractile function in human arteries *in vitro*

I. TSUNEYOSHI, Y. KANMURA AND N. YOSHIMURA

Summary

We have studied the effect of methylprednisolone on endotoxin-induced depression of contractile function in human gastroepiploic arteries. Endotoxin diminished the contractile response to noradrenaline in both the presence and absence of endothelium. This attenuation began after 4 h and reached a maximum after 10 h of endotoxin exposure. The cGMP content of endotoxin-treated rings was approximately seven-fold higher than in control rings. These endotoxin-mediated responses were blocked by L-NAME and methylene blue. These data indicate that the main cause of vascular hyposensitivity to noradrenaline was massive generation of nitric oxide. Pretreatment with methylprednisolone at concentrations (2.0–20.0 μg ml^{-1}) similar to those achieved in plasma after therapeutic administration dose-dependently inhibited these endotoxin-mediated responses. These data support the concept that pharmacological administration of methylprednisolone has the potential to prevent endotoxin-induced depression of the contractile response to noradrenaline seen in endotoxaemic shock. (*Br. J. Anaesth.* 1996; **76**: 251–257)

Key words

Polypeptides, endotoxin. Arteries. Hormones, glucocorticoid. Sympathetic nervous system, catecholamines.

Prolonged exposure of arterial tissue to endotoxin or to any of several cytokines has been shown to suppress its normal contractile response to cathecholamines [1]. Recent reports suggest that α adrenergic desensitization in inflammatory conditions is not mediated by changes in the number of receptors or their affinity for agonists, but may be caused by excessive production of endogenous nitric oxide (NO) [2–4]. There is strong evidence that inhibition of NO production may reverse the vascular hyporeactivity to pressor agents seen in patients with septic shock [5, 6].

NO is synthesized from the amino acid L-arginine through activation of NO synthase (NOS). It increases cellular levels of guanosine 3′, 5′-cyclic monophosphate (cGMP) which then induces vasorelaxation [7]. Two distinct forms of NOS have been identified in vascular tissues; these have been designated "constitutive" and "inducible" forms of NOS. Constitutive NOS (cNOS) is present in endothelium and contributes to vasodilatation under normal conditions [7]. The inducible form (iNOS) is expressed mainly in smooth muscle cells several hours after stimulation by a variety of stimuli, such as endotoxin or cytokines, and induces the production of a large amount of NO [8–10]. This raises the possibility that this enzyme may play a major role in vascular desensitization to pressor agents, leading to profound hypotension during inflammatory conditions. For this reason, pharmacological manipulation of iNOS might prove clinically useful in mitigating the abnormal vascular reactions in such conditions.

Expression of iNOS was found to be inhibited by the protein synthesis inhibitor cycloheximide [9]. Aminoguanidine, which is a nucleophilic hydrazine, was found to inhibit the relaxation of arterial rings from endotoxin-treated rats [11]. Moreover, iNOS requires tetrahydrobiopterin as a co-factor and inhibition of tetrahydrobiopterin synthesis was found to abolish endotoxin-induced NOS production in rat aortic smooth muscle cells [12]. However, cycloheximide has several severe side effects and other potentially useful drugs are as yet unlicensed and have still to undergo formal toxicological studies.

Glucocorticoids have also been shown to inhibit the expression of iNOS in several species [9, 13], indicating that the use of glucocorticoids may be useful in suppressing iNOS activity in humans. Although it has been suggested that glucocorticoids may have the capacity to prevent or suppress the development of cardiovascular collapse [14], not enough is known about the usefulness of glucocorticoids as potential inhibitors of the overproduction of NO evoked by endotoxin in human arteries.

In the present study, we investigated the effect of methylprednisolone, at concentrations within the range of serum concentrations reached during i.v. infusion of methylprednisolone 30 mg kg^{-1} in adult humans, on endotoxin-induced attenuation of noradrenaline-induced contraction in human gastroepiploic arteries *in vitro*. In addition, we measured cGMP concentrations in the same vascular tissues as an index of NOS activity.

ISAO TSUNEYOSHI, MD, YUICHI KANMURA, MD, NOZOMU YOSHIMURA, MD, Department of Anesthesiology and Critical Care Medicine, Kagoshima University School of Medicine, 8-35-1 Sakuragaoka, Kagoshima 890, Japan. Accepted for publication: September 5, 1995.

Correspondence to I.T.

This article is accompanied by an Editorial.

Materials and methods

PREPARATION

With the approval of the Ethics Committee of Kagoshima University School of Medicine, the omentum was resected from the stomach of each of 42 patients immediately after gastrectomy had been performed under general anaesthesia; each omentum was stored in oxygenated Krebs solution. The patients, who were all less than 70 yr old (mean 65.8 (range 38–69) yr) and who had suffered from gastric cancer, had no vascular disease or other complications. Furthermore, none had taken any anti-inflammatory drugs, such as aspirin or steroids, or vasoactive drugs before operation. Thirty minutes or less after the omentum had been resected, the gastroepiploic arteries were isolated in a dissecting chamber filled with Krebs solution, and fat and connective tissue removed carefully under a binocular microscope. Two vascular rings of length 2 mm were prepared from each artery for tension recording. One ring was carefully denuded of endothelium by inserting a small forceps into the lumen and gently rolling the ring backwards and forwards in the dissecting chamber. The lack of a functional endothelium was confirmed by the absence of endothelium-dependent relaxation of noradrenaline-induced contractions normally induced by acetylcholine 1×10^{-5} mol litre^{-1}.

ORGAN CHAMBER EXPERIMENTS

Mechanical activity in the human gastroepiploic arterial rings was assessed using a strain gauge (UL-100GR, Minebea, Tokyo) with the ring in a tissue bath filled with Krebs solution bubbled continuously with 95 % oxygen: 5 % carbon dioxide. The bath had a volume of 1.0 ml and the temperature of the solution was maintained at 37 °C. Krebs solution was infused continuously at a rate of 1 ml min^{-1} by a pump (Perista pump SJ-1211, ATTO, Tokyo) from one end of the bath and aspirated simultaneously by a water pump from the other. Resting tension was set at a value (20 mN) shown by the length–tension relationship to allow maximal active tension to be induced by noradrenaline 1.0 µmol litre^{-1}. The contractile response was measured as the maximum amplitude of the phasic response read from the pen recorder, and the response at the beginning of the experiment was normalized as a value of 1.0 for each ring. After 2 h of equilibrium in Krebs solution, noradrenaline 1.0 µmol litre^{-1} was applied to the vascular rings for 7 min every 30 min. After the amplitude of the contraction induced by noradrenaline 1.0 µmol litre^{-1} had become constant, endotoxin 10 µg ml^{-1} (lipopolysaccharide) was applied to the tissue by adding it to the Krebs solution. Other agents (N^G-nitro-L-arginine-methyl ester (L-NAME), methylene blue) were infused in Krebs solution so that the tissue was exposed to the dose indicated in the text. To determine the effect of glucocorticoid on endotoxin-induced attenuation of the evoked contractions, methylprednisolone was added in Krebs solution at a concentration of 20.0, 2.0 or 0.2 µg ml^{-1}. The arterial rings were immersed in medium containing methylprednisolone just after being prepared and throughout the experiment. To study the effect of glucocorticoids on ongoing endotoxin-induced attenuation, methylprednisolone 20.0 µg ml^{-1} was added 6 h after the start of some experiments, when attenuation induced by endotoxin had already begun.

ASSAY OF CGMP

After fat and connective tissue had been removed, gastroepiploic arterial rings (weight 30–50 mg) with the endothelium intact were allowed to equilibrate for 1 h in beakers containing Krebs solution bubbled with 95 % oxygen: 5 % carbon dioxide. One of the rings was then incubated with endotoxin 10 µg ml^{-1} and the other with either endotoxin 10 µg ml^{-1} with methylprednisolone 20 µg ml^{-1}, endotoxin 10 µg ml^{-1} with L-NAME 1 mmol litre^{-1} or endotoxin 10 µg ml^{-1} with methylene blue 10 µmol litre^{-1}. Approximately 12 h later, the phosphodiesterase inhibitor, 3-isobutyl-1-methylxanthine (IBMX) 100 µmol litre^{-1} was added to each preparation, 30 min before cGMP determination and then each ring was homogenized rapidly in a glass homogenizer. cGMP was extracted from the homogenate using trichloroacetic acid and the amount of cGMP in the extract measured using a cGMP enzyme immunoassay kit (Amersham International, Little Chalfont, UK).

SOLUTIONS

The composition of the Krebs solution was as follows (mmol litre^{-1}): Na^+ 137.4, K^+ 5.9, Mg^{2+} 1.2, Ca^{2+} 2.6, HCO_3^- 15.5, $H_2PO_4^-$ 1.2, CL^- 134.4 and glucose 11.5. All solutions contained indomethacin 10 µmol litre^{-1} to prevent the effects of prostanoids and L-arginine 200 µmol litre^{-1} as a substrate for NOS. They were bubbled with 95 % oxygen: 5 % carbon dioxide which adjusted the pH to 7.4. As contamination with endotoxin may be assumed to be substantial even in solutions made using distilled water, we used sterilized glassware and endotoxin-free water obtained from Ostuka Chemical Co. (Tokyo).

The chemicals used were: noradrenaline bitartrate, acetylcholine chloride, endotoxin (lipopolysaccharide: *E. coli* 055: B5), methylprednisolone, methylene blue, L-arginine and indomethacin, all form Sigma Chemical Company (St Louis, MO, USA), and N^G-nitro-L-arginine methyl ester (L-NAME) from Funakoshi (Tokyo, Japan).

STATISTICAL ANALYSIS

Results are expressed as mean (SD). The amplitude of the contraction induced by noradrenaline at the start of the experiment was normalized as a relative tension of 1.0 for each ring. Differences between the endotoxin-treated and methylprednisolone-treated groups were evaluated by analysis of variance. If significant differences were detected, Student's unpaired *t* test was used. To evaluate the dose-

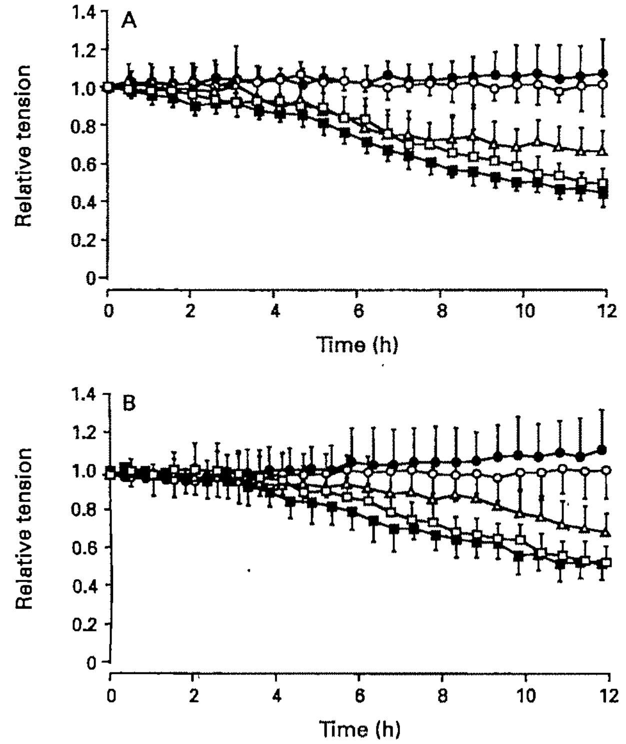


Figure 1 Effect of endotoxin 10 µg ml^{-1} on noradrenaline 1.0 µmol litre^{-1}-induced contractions and concentration-dependent effects of methylprednisolone on endotoxin-induced attenuation in endothelium-intact (A) and endothelium-denuded (B) rings from human gastroepiploic (mean, SD). Noradrenaline 1.0 µmol litre^{-1} was applied to the vascular rings for 7 min every 30 min over a 12-h period. The maximum amplitude of noradrenaline-evoked contraction at the start of the experiment was normalized as a relative tension of 1.0 for each arterial ring. Methylprednisolone treatment was begun before, and continued throughout application of endotoxin (which was begun at time 0). A: Noradrenaline-induced contraction with (■) or without (●) endotoxin 10 µg ml^{-1} treatment in endothelium-intact arteries. In endotoxin-treated rings, methylprednisolone prevented the attenuation of contraction in a dose-dependent manner (20.0 µg ml^{-1} (○), 2.0 µg ml^{-1} (△), 0.2 µg ml^{-1} (□)) ($n = 7$). B: Similar experiment in endothelium-denuded arteries (details as in (A)).

dependency of the effect of methylprednisolone, regression analysis was conducted with replication and Spearman rank correlation coefficients. Probabilities less than 5% ($P < 0.05$) were considered significant.

Results

EFFECT OF ACETYLCHOLINE ON NORADRENALINE-INDUCED CONTRACTION

When a functional endothelium is present, but not when it is absent, noradrenaline-induced contractions can be relaxed by acetylcholine. In our rings with intact endothelium, acetylcholine 1×10^{-5} mol litre^{-1} relaxed the noradrenaline 1.0 µmol litre^{-1}-induced contraction to 58.8 (8.3)% ($P < 0.01$, Student's unpaired t test, $n = 42$; the amplitude of the noradrenaline 1.0 µmol litre^{-1}-induced maximal contraction being normalized as 100%). On the other hand, in our endothelium-denuded rings, acetylcholine-induced relaxation was not observed (95.0 (5.2)%, $n = 42$).

EFFECT OF ENDOTOXIN ON NORADRENALINE-INDUCED CONTRACTIONS

After 2 h equilibration of the tissues in Krebs solution, noradrenaline 1.0 µmol litre^{-1} was applied for 7 min every 30 min. After the response to noradrenaline 1.0 µmol litre^{-1} had become stable, endotoxin 10 µg ml^{-1} was applied for 12 h. In the absence of endotoxin, the amplitude of contraction induced by noradrenaline 1.0 µmol litre^{-1} in endothelium-intact rings remained stable for more than 12 h (after 12 h, 1.05 (0.17) times the initial maximal contraction, $n = 7$). Similarly, the amplitude of noradrenaline-induced contractions in endothelium-denuded rings was stable for 12 h (after 12 h, 1.16 (0.20), $n = 7$). Endotoxin 10 µg ml^{-1} gradually attenuated the noradrenaline-induced contractions over a long time period, both in endothelium-denuded and endothelium-intact rings (fig. 1). Thus after 12 h treatment with endotoxin 10 µg ml^{-1}, the amplitude of contraction was 0.43 (0.07) in endothelium-intact rings ($n = 7$) and 0.53 (0.09) in endothelium-denuded rings ($n = 7$). Table 1 shows the effect of 12-h exposure to endotoxin on the contraction induced by noradrenaline 1.0 µmol litre^{-1}, and the effect of an inhibitor of NOS, L-NAME 1.0 mmol litre^{-1} and that of an inhibitor of guanylate cyclase, methylene blue 10 µmol litre^{-1}. Endotoxin-induced relaxation was abolished by administration each of these drugs.

Table 1 Attenuation of noradrenaline-induced contraction induced by 12-h exposure to endotoxin and its inhibition by L-NAME or methylene blue (MB) (mean (SD)). The initial maximal contraction induced by noradrenaline is given the value 1.0. ** $P < 0.01$ compared with value after 12 h of noradrenaline-induced contractions (Student's t test)

	Relative tension		
		12.5 h after	
Sample ($n = 7$)	12 h after	L-NAME (1 mmol litre^{-1})	MB (10 µmol litre^{-1})
Control			
Endothelium intact	1.05 (0.17)	1.06 (0.21)	1.05 (0.13)
Endothelium denuded	1.16 (0.20)	1.28 (0.17)	1.15 (0.24)
Endotoxin 10 µg ml^{-1} added			
Endothelium intact	0.43 (0.07)	0.92 (0.17)**	1.03 (0.15)**
Endothelium denuded	0.53 (0.09)	0.91 (0.14)**	0.92 (0.13)**

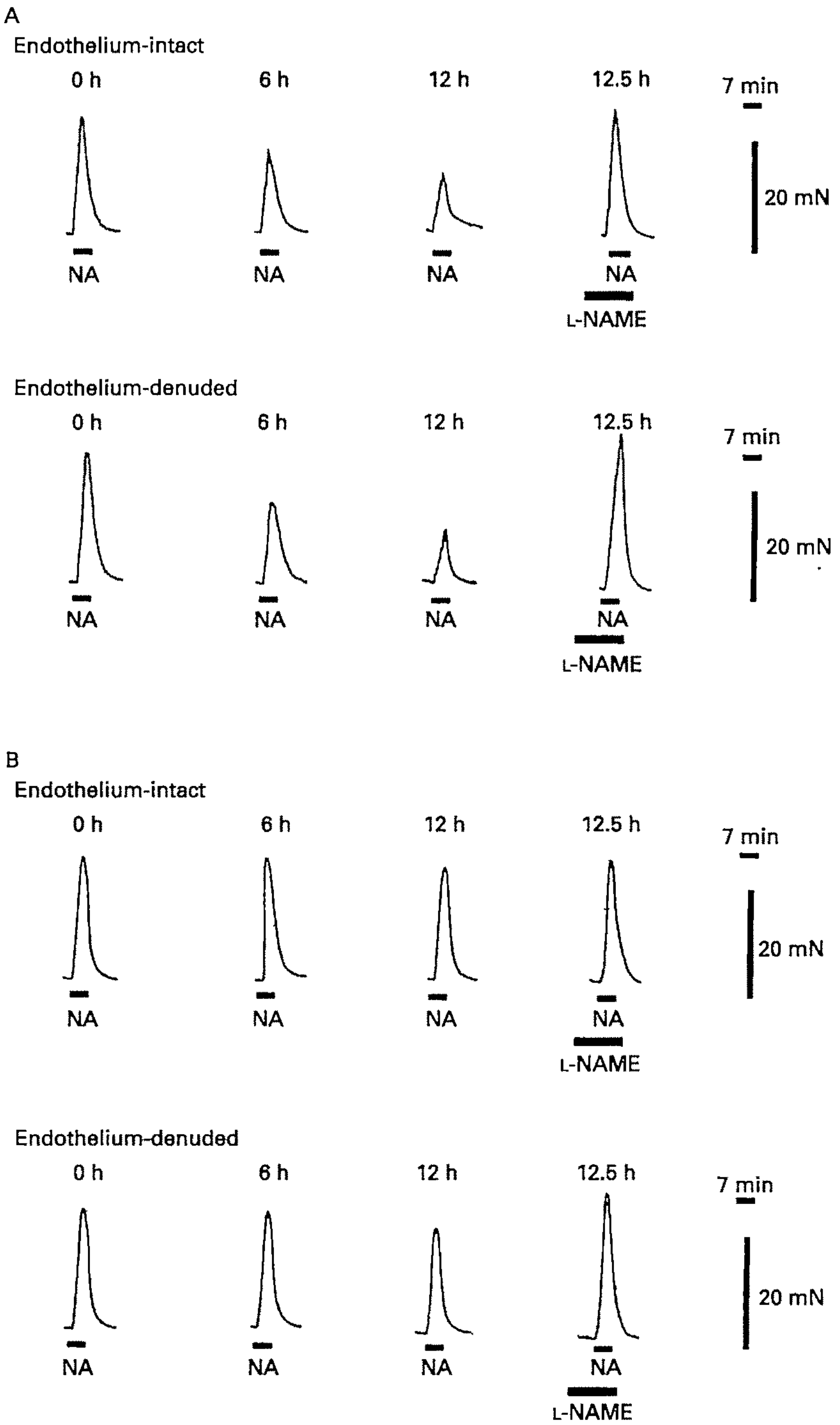


Figure 2 Typical examples of the effect of methylprednisolone 20 μg ml^{-1} on endotoxin 10 μg ml^{-1}-induced attenuation of contraction in endothelium-intact and endothelium-denuded rings from human gastroepiploic arteries. Noradrenaline (NA) 1.0 μmol $litre^{-1}$ was applied to the vascular rings for 7 min every 30 min over a 12-h period. A: Effect of endotoxin 10 μg ml^{-1} (begun at time 0) on contractions induced by NA 1.0 μmol $litre^{-1}$. Endotoxin-treatment was continued for 12 h and then L-NAME 1.0 mmol $litre^{-1}$ was applied. B: Effect of methylprednisolone 20 μg ml^{-1} on the attenuation of contraction induced by endotoxin 10 μg ml^{-1}. Methylprednisolone was present throughout the 12-h incubation.

EFFECT OF METHYLPREDNISOLONE ON ENDOTOXIN-INDUCED ATTENTION OF CONTRACTION

Endotoxin-induced inhibition of noradrenaline-induced contraction was reduced or abolished by methylprednisolone in a dose-dependent manner. Figure 2 shows typical records of contractions induced by noradrenaline 1.0 μmol $litre^{-1}$ in endotoxin 10 μg ml^{-1}-treated rings and in rings treated with both endotoxin and methylprednisolone 20 μg ml^{-1}. After treatment with endotoxin had been in progress for 6 or 12 h, the noradrenaline-induced contraction was reduced significantly in both endothelium-intact and endothelium-denuded rings. This inhibition was prevented in both types of ring when methylprednisolone 20 μg ml^{-1} was present in the medium throughout the experiment, the amplitude of contraction remaining constant for 12 h

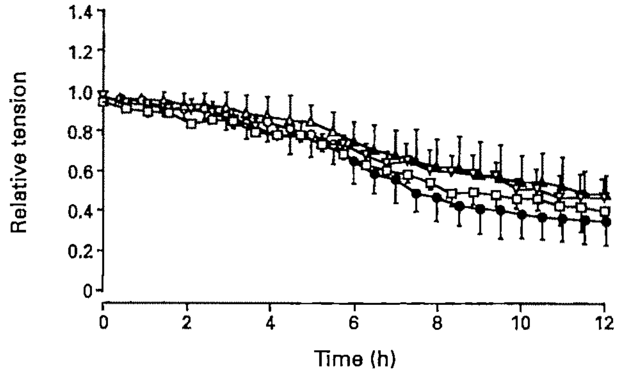


Figure 3 Effect of delayed application of methylprednisolone 20 μg ml^{-1} on the attenuation of contraction induced by endotoxin 10 μg ml^{-1} (mean, SD). Endotoxin 10 μg ml^{-1} was applied to endothelium-intact (○, □) and endothelium-denuded (△, ▽) rings from human gastroepiploic arteries for 12 h. In some experiments, methylprednisolone 20 μg ml^{-1} was present for the second 6-h period only in endothelium-intact (●) and endothelium-denuded (▲) arterial rings ($n = 7$).

(fig. 1). In contrast, a low concentration of methylprednisolone (0.2 μg ml^{-1}) in Krebs solution had no effect on the attenuation induced by endotoxin (endothelium-intact arteries: 0.48 (0.09); endothelium-denuded arteries: 0.54 (0.09), both after 12 h, $P > 0.05$). A moderate concentration of methylprednisolone (2.0 μg ml^{-1}) had a preventative effect that was slight but significant (endothelium-intact arteries: 0.65 (0.14); endothelium-denuded arteries: 0.68 (0.11), both after 12 h, $P < 0.05$). The corresponding values with methylprednisolone 20.0 μg ml^{-1}, showing complete inhibition, were: endothelium-intact arteries: 1.04 (0.21); endothelium-denuded arteries: 0.99 (0.15) ($P < 0.01$). On the other hand, in control rings not treated with endotoxin, methylprednisolone did not modify the contractions evoked by noradrenaline 1.0 μmol litre^{-1} (endothelium-intact arteries: 1.10 (0.21); endothelium denuded arteries: 1.02 (0.14), both after 12 h, $P < 0.05$).

Figure 3 shows the effect of methylprednisolone 20.0 μg ml^{-1} when applied to endotoxin-treated rings for only 6 h, beginning 6 h after the start of the experiment. Such delayed addition of methylprednisolone 20 μg ml^{-1} was ineffective after the attenuation induced by endotoxin commenced. At the end of 12 h, the relative tension values induced by noradrenaline were: endothelium-intact rings, 0.46 (0.12) without methylprednisolone, 0.40 (0.11) with methylprednisolone ($P > 0.05$, $n = 7$); endothelium-denuded rings, 0.51 (0.08) without methylprednisolone, 0.52 (0.10) with methylprednisolone ($P > 0.05$, $n = 7$).

CHANGES IN CGMP CONTENT OF VASCULAR TISSUES

We chose to measure the cGMP content of rings with intact endothelium as their status was probably closer to that of normal blood vessels. Endotoxin greatly increased the amount of cGMP in rings with intact endothelium cut from human gastroepiploic arteries. The measured amounts of cGMP were: before exposure to endotoxin, 223.2 (78.6) fmol/mg protein and after 12 h application of endotoxin, 1628.6 (790.0) fmol/mg protein ($P < 0.05$, $n = 6$). This endotoxin-induced increase in cGMP content was blocked by methylene blue 10 μmol litre^{-1} (cGMP content 52.9 (74.1) fmol/mg protein, $P > 0.05$, $n = 6$) and by L-NAME mmol litre^{-1} (cGMP content 256.3 (66.8) fmol/mg protein, $P > 0.05$, $n = 6$). The increase in cGMP content in endotoxin-treated rings was also prevented by continuous application of methylprednisolone 20 μg ml^{-1} (cGMP content 339.7 (197.5) fmol/mg protein, $P > 0.05$, $n = 6$) (fig. 4).

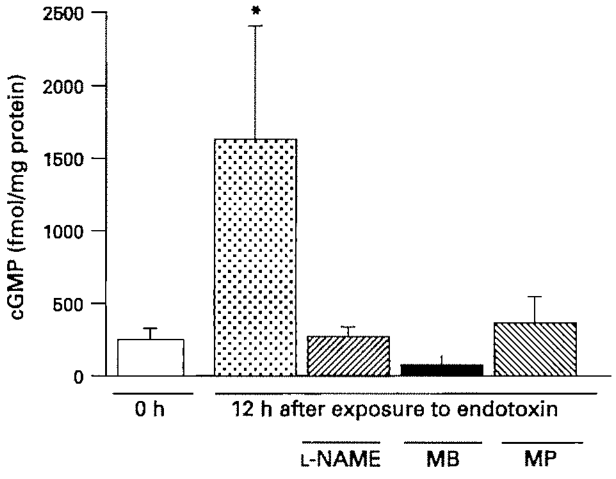


Figure 4 Effects of endotoxin 10 μg ml^{-1} (□), N^G-nitro-L-arginine methyl ester (L-NAME) 1.0 mmol litre^{-1} (▨), methylene blue (MB) 10 μmol litre^{-1} (■) and methylprednisolone (MP) 20 μg ml^{-1} (▧) on cGMP content in human gastroepiploic arteries with the endothelium intact (mean, SD). One of a pair of rings was incubated with endotoxin 10 μg ml^{-1} and the other with either endotoxin 10 μg ml^{-1} with MP 20 μg ml^{-1}, endotoxin 10 μg ml^{-1} with L-NAME mmol litre^{-1} or endotoxin 10 μg ml^{-1} with MB 10 μmol litre^{-1}. Each inhibitor was applied for 1 h before and throughout the experiment. IBMX 100 μmol litre^{-1} was added to each solution 30 min before cGMP determination ($n = 7$). $^*P < 0.05$ compared with amount of cGMP at 0 h.

Discussion

These results demonstrate that pretreatment of isolated human vascular tissues with methylprednisolone inhibits, in a concentration-dependent manner, endotoxin-evoked depression of the contractile response to noradrenaline. This inhibitory activity of methylprednisolone was seen at concentrations as low as those achieved in plasma after therapeutic administration.

In the present study, contractions of arteries elicited by noradrenaline remained more or less constant throughout each experiment in the absence of endotoxin, suggesting that the anaesthetics and neuromuscular blocking drugs used did not alter vasoreactivity under the experimental conditions. On the other hand, in arterial rings exposed to endotoxin 10 μg ml^{-1}, noradrenaline-induced contractions showed a gradual decrease in tension both in the presence and absence of endothelium for several hours after the initial exposure to endotoxin. These results indicate that noradrenaline-induced contraction, which occurs via stimulation of α adrenergic receptors, was depressed easily by endotoxin. Moreover, this effect of endotoxin was reversed by the NO inhibitor, L-NAME, and by the guanylate cyclase inhibitor, methylene blue. Consequently, we conclude that endotoxin evoked massive production of NO, and thus diminished the contractile response to noradrenaline. A similar conclusion was reached after experiments on rat aortic rings incubated with endotoxin [15]. Indeed, it was demonstrated that the reduced sensitivity to catecholamines in endotoxaemic rats was caused by overproduction of endogenous NO [2, 3].

Endotoxin also increased the intracellular concentration of cGMP in our arterial tissues, the content of cGMP in rings treated with endotoxin for 12 h being about seven-fold greater than that in control rings. This effect of endotoxin was blocked also by both methylene blue and L-NAME. These studies with inhibitors indicate that the increase in cGMP evoked by endotoxin may result from activation of a soluble form of guanylate cyclase. Previous reports by other authors have also indicated that release of NO from vascular walls activates guanylate cyclase, producing cGMP [2–4]. The mechanisms by which cGMP evokes smooth muscle relaxation have been studied [16–18] and the conclusion reached that increased smooth muscle cGMP content is associated with a reduced intracellular calcium level. Thus, these results may explain the endotoxin-induced reduction in sensitivity to noradrenaline, as the response of vascular smooth muscle to α adrenergic agents is dependent mainly on the concentration of free Ca^{2+} in the myoplasm [19].

The interaction of glucocorticoids with cardiovascular tissue has been shown to play an important role in cardiovascular function. It is clear that they potentiate the constrictor response of vascular smooth muscle to catecholamines after several days' exposure, although there is still no consensus on the exact mechanisms involved [20–22]. Interestingly, recent data have indicated that glucocorticoids inhibit induction of iNOS in vascular tissue and reduced the sustained hypotension induced by endotoxin in animal experiments [23–25]. In our experiment, the glucocorticoid methylprednisolone, partially or completely prevented, in a dose-dependent manner, endotoxin-induced diminution of the contractile response to noradrenaline. Additionally, accumulation of cGMP in endotoxin-treated human arterial rings was blocked by the presence of methylprednisolone 20.0 $\mu g\ ml^{-1}$. These results suggest that methylprednisolone suppressed endotoxin-induced expression of iNOS and thus prevented endotoxin-induced depression of sensitivity to noradrenaline in human arteries.

These preventative effects of methylprednisolone in our *in vitro* study support the concept that the drug could be used as a therapeutic agent for reducing or preventing the vascular hyporeactivity mediated by endotoxin. The concentration of methylprednisolone in human plasma has been reported to reach a maximum of 20.0 $\mu g\ ml^{-1}$ just after i.v. administration of 30 $mg\ kg^{-1}$ in the adult human. There was a rapid decrease for approximately 12 h (12 h after injection, the concentration was about 2.0 $\mu g\ ml^{-1}$) and then a slower decline over the next 12 h [26]. In our experiments, methylprednisolone 20.0 $\mu g\ ml^{-1}$ completely prevented the attenuation of contraction induced by endotoxin and methylprednisolone 2.0 $\mu g\ ml^{-1}$ reduced it slightly but significantly, while 0.2 $\mu g\ ml^{-1}$ had no effect. The effective concentration of methylprednisolone used here correlates well with the serum concentrations found during the first 12 h after i.v. infusion of methylprednisolone 30 $mg\ kg^{-1}$ in the adult human. Therefore, i.v. infusion of 30 $mg\ kg^{-1}$ should have the potential to prevent or reduce the desensitization to cathecholamines induced by endotoxin in human arteries.

However, in our study, when methylprednisolone 20 $\mu g\ ml^{-1}$ was given after the attenuation of contraction induced by endotoxin had started, it failed to elicit inhibition. A recent report by Marumo and colleagues [27] has suggested that, in rat cultured smooth muscle cells, glucocorticoids act by directly inhibiting expression of the iNOS gene, rather than by reducing its enzymatic activity (which persists for several days) [9]. These results suggest that when iNOS has been induced sufficiently by endotoxin, methylprednisolone might be unable to exert a preventative effect on the generation of NO, which would already have been raised by the increase in iNOS. Therefore, methylprednisolone might need to be given before, or shortly after, exposure to the bacterial pathogens that produce endotoxin.

Glucocorticoids have powerful immunosuppressive and anti-inflammatory actions and are pharmacologically useful in the treatment of various diseases. However, there is still considerable controversy on their use in the treatment of severe sepsis or septic shock [28, 29]. A recent report has warned of the possible adverse effects of methylprednisolone in the treatment of critically ill patients [30]. On the other hand, a massive dose of methylprednisolone 30 $mg\ kg^{-1}$ repeated once after 4 h if the patient remains unstable has been reported to reduce early mortality and circulatory failure in septic shock [28]. Our results support the concept of a beneficial effect of methylprednisolone on the vascular hyporeactivity associated with immunologically released NO in humans. Moreover, as recent data provide strong evidence of an important role for mediators such as cytokines or phagocytic cells in the pathogenesis of septic shock [31], the desirable immunosuppressive effects of glucocorticoids may include a direct cytotoxic action. Thus the efficacy of glucocorticoids in septic conditions may depend on the balance between their protective and deleterious roles.

Acknowledgements

We thank Professor T. Itoh (Department of Pharmacology, Nagoya City University Medical School), T. Sameshima, J. Miyao (Department of Anaesthesiology and Critical Care Medicine, Kagoshima University School of Medicine) and the directors of Kagoshima Medical Association Hospital. We also thank Dr R. J. Timms for his help in preparing the manuscript.

References

1. Wakabayashi I, Hatake K, Kakishita E, Hisida S, Nagai K. Desensitization of alpha-1 adrenergic receptor mediated smooth muscle contraction in aorta from endotoxic rats. *Life Science* 1989; 45: 509–515.

2. Moritoki H, Takeuch S, Hisayama T, Kondoh W. Nitric oxide synthase responsible for L-arginine-induced relaxation of rat aortic rings in vitro may be an inducible type. *British Journal of Pharmacology* 1992; **107**: 361–366.
3. Julou-Schaeffer G, Gray G, Fleming I. Loss of vascular responsiveness induced by endotoxin involves L-arginine pathway. *American Journal of Physiology* 1990; **259**: H1038–H1043.
4. Beasley D. Interleukin 1 and endotoxin activate soluble guanylate cyclase in vascular smooth muscle. *American Journal of Physiology* 1990; **259**: R38–R44.
5. Petros A, Bennett D, Vallance P. Effect of nitric oxide synthase inhibitor on hypotension in patients with septic shock. *Lancet* 1991; **338**: 1557–1558.
6. Geroulanos S, Schilling J, Cakmakci M, Jung H, Largiader F. Inhibition of NO synthesis in septic shock. *Lancet* 1992; **339**: 434–435.
7. Moncada S, Palmer RMJ, Higgs EA. Nitric oxide: physiology, pathophysiology and pharmacology. *Pharmacology Reviews* 1991; **43**: 109–142.
8. Koide M, Kawahara Y, Tsuda T, Yokoyama M. Cytokine-induced expression of an inducible type of nitric oxide synthase gene in cultured vascular smooth muscle cells. *FEBS Letters* 1993; **318**: 213–217.
9. Radpmski MW, Palmer RMJ, Moncada S. Glucocorticoids inhibit the expression of an inducible, but not the constitutive, nitric oxide synthase in vascular endothelial cells. *Proceedings of the National Academy of Sciences USA* 1990; **87**: 10043–10047.
10. Salvemini D, Korbut R. Immediate release of nitric oxide-like factor from bovine aortic endothelial cells by Escherichia coli lipopolysaccharide. *Proceedings of the National Academy of Sciences USA* 1990; **87**: 2593–2597.
11. Griffiths MJD, Messent M, MacAllister RJ, Evans TW. Aminoguanidine selectively inhibits inducible nitric oxide synthase. *British Journal of Pharmacology* 1993; **110**: 963–968.
12. Gross SS, Levi R. Tetrahydrobiopterin: an absolute requirement for cytokine-induced nitric oxide generation by vascular smooth muscle. *Journal of Biological Chemistry* 1992; **267**: 25722–25729.
13. Kanno K, Hirata Y, Imai T, Marumo F. Induction of nitric oxide synthase gene by interleukin in vascular smooth muscle cells. *Hypertension* 1993; **22**: 34–39.
14. Robert CHJ. Adrenocorticotropic hormone, adrenocortical steroids and their synthetic analogs: inhibitors of the synthesis and actions of adrenocortical hormones. In: Gilman AG, Theodore WR, Alan SN, Palmer T, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th Edn. New York, Macmillan, 1990; 1431–1462.
15. Fleming I, Gray GA, Julou-Schaeffer G, Parratt JR, Stoclet J-C. Incubation with endotoxin activates the L-arginine pathway in vascular tissue. *Biochemical and Biophysical Research Communications* 1990; **171**: 562–568.
16. Rapoport RM. Cyclic guanosine monophosphate inhibition of contraction may be mediated through inhibition of phosphatidylinositol hydrolysis in rat aorta. *Circulation Research* 1986; **58**: 407–410.
17. Furukawa KI, Ohshima N, Iwata YT, Shigekawa M. Cyclic GMP stimulates Na^+/Ca^{2+} exchange in vascular smooth muscle cells in primary culture. *Journal of Biological Chemistry* 1991; **266**: 12337–12341.
18. Twort CHC, van Breemen C. Cyclic guanosine monophosphate-enhanced sequestration of Ca^{2+} by sarcoplasmic reticulum in vascular smooth muscle. *Circulation Research* 1988; **62**: 961–964.
19. Itoh T, Ikebe M, Kargacin GJ, Harsthorne DJ, Kemp BE, Fay FS. Effects of modulators of myosin light-chain kinase activity in single smooth muscle cells. *Nature (London)* 1989; **338**: 164–167.
20. Yasunari K, Kohono M, Balmfort A, Murakawa K, Yokokawa K, Kurihara N, Takeda T. Glucocorticoids and dopamine-1 receptors on vascular smooth muscle cells. *Hypertension* 1989; **13**: 575–581.
21. Sato A, Suzuki H, Iwaita Y, Nakazato Y, Kato H, Saruta T. Potentiation of inositol trisphosphate production by dexamethasone. *Hypertension* 1992; **19**: 109–115.
22. Kornel L, Manisundaram B, Nelson WA. Glucocorticoids regulate Na^+ transport in smooth vascular muscle through the glucocorticoid receptor-mediated mechanism. *American Journal of Hypertension* 1993; **6**: 736–744.
23. Rees DD, Cellek RMJ, Palmer RMJ, Moncarda S. Dexamethasone prevents the induction by endotoxin of a nitric oxide synthase and the associated effects on vascular tone: an insight into endotoxic shock. *Biochemical and Biophysical Research Communications* 1990; **173**: 541–547.
24. Di Rosa M, Radomski MW, Carnuccio R, Moncada S. Glucocorticoids inhibit the induction of nitric oxide synthase in macrophages. *Biochemical and Biophysical Research Communications* 1990; **172**: 1246–1252.
25. Knowles RG, Salter M, Brooks SL, Moncada S. Anti-inflammatory glucocorticoids inhibit the induction by endotoxin of nitric oxide synthase in the lung, liver and aorta of the rat. *Biochemical and Biophysical Research Communications* 1990; **172**: 1042–1048.
26. Stubbs SS. Corticosteroids and bioavailability. *Transplantation Proceedings* 1975; **7**: 11–19.
27. Marumo T, Nakaki T, Nagata K, Miyata M, Adachi H, Esumi H, Suzuki H, Saruta T, Kato R. Dexamethasone inhibits nitric oxide synthase mRNA induction by interleukin-1α and tumor necrosis factor-α in vascular smooth muscle cells. *Japanese Journal of Pharmacology* 1993; **63**: 361–367.
28. Sprung CL, Caralis PV, Marcial EH. The effect of high dose corticosteroids in patients with shock. A prospective, controlled study. *New England Journal of Medicine* 1984; **18**: 1137–1143.
29. Veterans Administration System Cooperative Study Group. Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. *New England Journal of Medicine* 1987; **317**: 695–665.
30. The Methylprednisolone Severe Sepsis Study Group. Detrimental effects of high-dose methylprednisolone sodium succinate on serum concentrations of hepatic and renal function indicators in severe sepsis and septic shock. *Critical Care Medicine* 1993; **21**: 191–195.
31. Anthony FS. Current prospects for the treatment of clinical sepsis. *Critical Care Medicine* 1994; **22**: S12–S18.

British Journal of Anaesthesia 1996; 76: 258–265

Central nuclei and spinal pathways in feedback inhibitory spinal cord potentials in ketamine-anaesthetized rats

S. DENDA, K. SHIMOJI, M. TOMITA, H. BABA, T. YAMAKURA, H. MASAKI, H. ENDOH AND S. FUKUDA

Summary

It has been suggested that heterosegmentally activated slow positive potentials (HSP), recorded from the spinal cord of rat and humans, are feedback inhibitory potentials. The present study was carried out to define ascending and descending spinal tracts and the sites of central nuclei involved in the production of these HSP, and the effects of ketamine on these central nuclei. The spinal cords in ketamine-anaesthetized rats were transected to determine the ascending and descending tracts involved in the production of hindpaw (HP) and forepaw (FP) HSP, respectively. Lesions of the brain at various levels were performed stereotactically during ketamine anaesthesia. Dorsal one-third resection of the cord at the T8–9 level did not affect HSP significantly, while contralateral lesion of the dorsal two-thirds of the cord decreased FP–HSP but not HP–HSP during ketamine. Bilateral transection of the ventral one-third of the cord abolished both HSP. Ablation of the cerebral cortex, cerebellum, thalamus, midbrain and pons did not affect HSP significantly. However, transection of the middle medulla decreased, while transection of the most caudal part of the medulla completely abolished both HSP. Ketamine decreased HSP even in the medulla–spinal cord preparation and the segmental slow positive wave in spinalized animals. In ketamine-anaesthetized rats, ascending and descending spinal tracts involved in the production of HP–HSP and FP–HSP are located bilaterally in the ventrolateral quadrant and in the contralateral lateral funiculus and ventrolateral quadrant, respectively. Principal central nuclei feeding back HSP might be situated diffusely in the medulla down to the caudal part. Ketamine is suggested to suppress these inhibitory feedback potentials predominantly at, and partly even below, the level of the medulla. (*Br. J. Anaesth.* 1996; **76**: 258–265)

Key words

Anaesthetics i.v., ketamine. Monitoring, evoked potentials. Spinal cord, evoked potentials. Rat.

In addition to segmentally evoked spinal cord potentials (segSCP) produced in the segmental dorsal surface of the cord, slow positive potentials (heterosegmentally evoked slow positive potentials (HSP)) can be recorded from the heterosegmental dorsal surface of the spinal cord by peripheral skin nerve stimulation in ketamine-anaesthetized rats [1–3], and by large nerve trunk stimulation close to the cord in conscious humans [4, 5]. Physiological and pharmacological features of these HSP suggest that they reflect feedback inhibitory activities via supraspinal structures [1–3], probably feedback primary afferent depolarizations (PAD) [3], providing an important feedback control system of sensory transmission, including pain. Such HSP might also provide a tool for studying the mechanism of transcutaneous electric nerve stimulation (TENS) or electroacupuncture [5].

Previous studies in ketamine-anaesthetized rats [2] suggested that central nuclei which send the feedback impulses to the spinal cord thereby producing HSP may exist in more than one brain structure, as latencies of HSP showed inter-individual variation.

The present study was undertaken to determine the central feedback nuclei involved in the production of HSP, and also the sites of the effects of ketamine on these HSP in preparations containing principal central nuclei. We also tested which portions of the cord were responsible for ascending and descending tracts producing HSP in a specially designed preparation.

Materials and methods

Approval of the Institutional Committee on Animal Experimentation was obtained, and the institutional guidelines for use of laboratory animals were observed and followed during the present study.

The experiments were carried out in 23 adult male rats, weighing 300–350 g. The anaesthetic and surgical procedures were the same as those reported in previous studies [1–3] except for the additional experimental brain and spinal cord lesions. After i.p. injection of ketamine hydrochloride 120 mg kg^{-1} with atropine sulphate 0.1 mg kg^{-1}, a tracheal tube

---

SADAHEI DENDA, MD, KOKI SHIMOJI, MD, MISAO TOMITA, MD, HIROSHI BABA, MD, TOMOHIRO YAMAKURA, MD, HISASHI MASAKI, MD, HIROSHI ENDOH, MD, SATORU FUKUDA, MD, Department of Anaesthesiology, Niigata University School of Medicine, 1-757 Asahi-machi, Niigata 951, Japan. Accepted for publication: September 14, 1995.

Correspondence to K. S.

was introduced through a tracheostomy and connected to a Harvard animal ventilator. Tidal volume and frequency of 50–60 b.p.m. were adjusted to maintain a normal $P\text{E}'_{CO_2}$ of 4.5–5.3 kPa, monitored by a capnograph via a small polyethylene tube (250 μm in diameter) introduced into the orifice of the tracheal tube. The animals were paralysed by i.v. injection of pancuronium 0.2 mg kg^{-1} h^{-1}.

The left femoral artery and vein were cannulated to monitor arterial pressure, sample blood and permit infusion of Ringer's lactate solution 4 ml kg^{-1} h^{-1} with ketamine 30 mg kg^{-1} h^{-1} and fresh blood from another ketamine-anaesthetized rat when bleeding exceeded 20 ml kg^{-1} (25–30 % of total blood volume). Arterial blood samples (0.1 ml) were obtained at the time of cannulation, at the middle of the experimental procedures, at termination of the experiment and occasionally at the time of mass bleeding (in three cases) to check the adequacy of blood gases and packed cell volume (PCV). Three animals received 22–30 ml kg^{-1} of fresh blood even though evoked potentials were not affected significantly. Bleeding was controlled by light pressure with cotton or by gel foam. Blood loss was determined by the dilution method. Blood was sucked into a glass bottle through a stainless tube or absorbed in the gauze. Blood in the gauze was washed gently by a saline solution in another bottle, and PCV of the diluted blood in these two bottles was measured.

Preliminary experiments with electroencephalography (EEG) and somatosensory evoked potentials from the brain and spinal cord showed no significant changes with stable arterial pressure over a period of several hours during infusion of ketamine [1–3] at a rate which was adequate to suppress behavioural responses of the rat to surgical incision without administration of a neuromuscular blocker. A cannula was inserted also through a small skin incision into the urinary bladder to allow monitoring of urine volume. The electrocardiogram was monitored continuously through needle electrodes inserted into the s.c. tissue of the thorax. Rectal temperature was maintained at 37.0–38.0 °C by a homeothermic blanket system.

The animals were mounted on a stereotactic frame, and laminectomies were carried out on C5–6 and T8–L1 vertebrae to expose the cervical and thoracolumbar cord. The head was also secured gently in a stereotactic frame by ear bars.

Flexible ball-tip electrodes (Ag–AgCl) were placed gently on the cervical (C5) and lumbar (L5) cord surfaces by the floating method (spring mounting) at the midline. Reference electrodes were fixed to nearby bones. A needle electrode was placed at the left preorbital area with the reference electrode at the left ear to monitor the EEG and brain evoked potentials. The right forepaws and hindpaws were stimulated electrically by a stimulator (Nihon Kohden SEN-7103) through a constant current isolation unit at 1 Hz with silver–silver chloride needle electrodes (150 μm in diameter, 10 mm in length) inserted s.c. into the vestigial thumb and fourth digit on the forepaw and the first and fifth toes on the hindpaw. Stimulus (square wave monophasic pulse, 0.1 ms) intensity was adjusted to 2.5–10 × threshold strength (1.3–1.7 to 13–17 V) for the segmental negative cord dorsum potential (N1) so that it constantly produced slow positive waves in all animals. The same stimulus was applied to both fore- and hindpaws using a switch box. The stimulus intensity used was monitored in a preliminary study by recording the nerve action potentials from the sural nerve at the end of the experiments, and verified to evoke Aβ and Aδ fibre action potentials but not C fibre action potentials (13–17 V) [2]. All potential changes were averaged ($n = 50$) by a computer (ATAC 1300, Nihon Kohden) and plotted on an X–Y plotter.

The peak amplitudes of N1 and P2 components in the segSCP and those of HSP were measured from the background activity (see tables 1 and 2). The background activity (the pre-response baseline) was recorded in response to forepaw (FP) or hindpaw (HP) stimulation at the subthreshold strength in each experiment.

All evoked potential recordings were conducted under stable haemodynamics (mean arterial pressure (MAP) 70–105 mm Hg; heart rate (HR) 380–450 beat min^{-1}). A slight transient increase and an increase followed by a decrease in MAP and HR were sometimes observed during skin incision and spinal cord lesion, respectively, but not during electrical stimulations.

EXPERIMENT I: SPINAL CORD LESIONS

As shown in figure 1, transection of the spinal cord at the thoracic level destroyed the ascending tract for HP–HSP and that of the descending tract for FP–HSP, which was described originally by Villanueva and colleagues in their study on diffuse noxious inhibitory control (DNIC) [6]. Pilot studies showed that electrical coagulation methods extended substantially beyond the limit of the lesion to the surrounding tissues on histological examination. Therefore, we prepared small pieces of razors to insert perpendicularly from the dorsal surface of the spinal cord, and fixed the cord by injecting 10 % formalin i.v. at the end of the experiment for histological examination. Six pieces of razors were inserted into the cord, one by one, at the T8–T9 level, as shown in figure 1, 0.5 mm apart, from the caudal to the rostral sites after eliminating the arachnoid and pia maters with a fine pincette under light microscopy, and the evoked potentials were recorded following each additional lesion. The ventrodorsal axis (diameter) of the spinal cord was measured in preliminary experiments in five rats and the depth of insertion was determined as shown in figure 1. Differences between the stereotactically induced lesions and histological examination were within the range of 0.05 mm.

EXPERIMENT II: BRAIN LESIONS AND EFFECTS OF KETAMINE

After craniotomy and exposure of cerebral and cerebellar cortices, suction of brain tissue throughout the cerebral cortex and whole cerebellum was carried

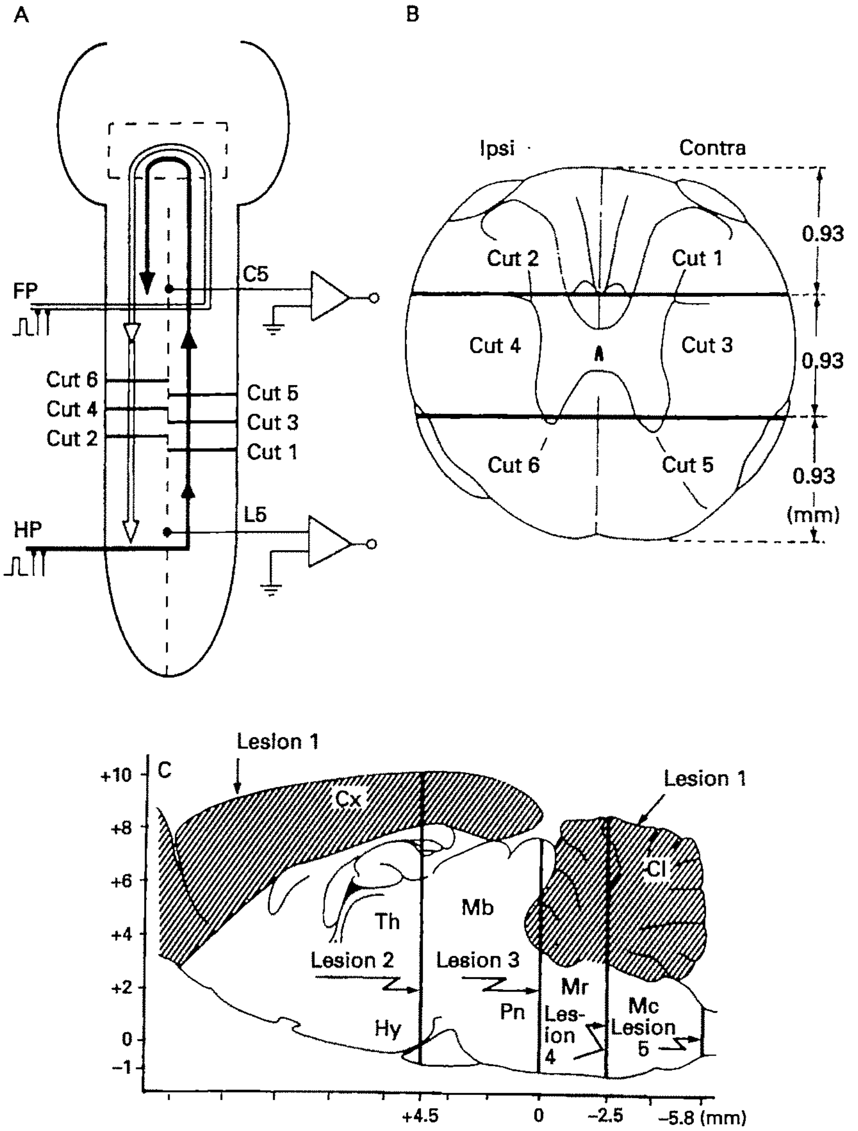


Figure 1 Schematic (A) and stereotactic (B, C) representations of experimental procedures. A: The spinal cord was transected at the T8–9 level so that the afferent tract for HSP evoked by hindpaw (HP) stimulation and the descending tract for that evoked by forepaw (FP) stimulation were blocked, respectively. B: The spinal cord was hemisected from the contralateral dorsal one-third (cut 1) to the ipsilateral ventral one-third, from caudal to rostral, 0.5 mm apart, as shown in (A). Small pieces of razors were inserted stereotactically, one by one, from the dorsal surface of the cord at 0.93-mm steps. C: The brain lesion was carried out as described in the text from lesion 1 to lesion 5. Lesion 1 = resection of whole cerebral cortex and cerebellum; lesion 2 = resection between the thalamus, including the hypothalamus and the midbrain, at AP+4.5, according to the atlas of Paxinos and Watson [7]; lesion 3 = transection between the pons and medulla oblongata at AP±0; lesion 4 = transection at the middle part of the medulla at AP−2.5; lesion 5 = transection at the most caudal part of the medulla oblongata at AP−5.75 mm.

out with the assistance of a bipolar blood coagulation apparatus under a stereotactic microscope.

The thalamus with the underlying hypothalamus was resected at the level of AP+4.5 mm (fig. 1) using a plate with a sharpened edge, leaving the most part of the midbrain according to the stereotactic brain map of Paxinos and Watson [7]. The midbrain and pons were severed at the level of AP±0 mm, leaving the medulla intact. Transection was performed at the level of the middle medulla, AP−2.5 (fig. 1). Finally, the most caudal part of the medulla was transected at the level of AP−5.75 mm, thus separating the whole medulla from the spinal cord (fig. 1) [7]. In the latter part of the experiment (in six of 14 animals), the third and fourth transections were conducted initially, as the first to third procedures did not affect HSP.

The third and fourth procedures sometimes caused transient hypotension and arrhythmia (two and one in the third and fourth sections, respectively) which recovered fully within 2–5 min with Ringer's lactate solution, or blood, or both, and no pharmacological intervention.

Evoked potential recordings were performed at least 30 min after each step of brain lesion, as the evoked potentials sometimes showed transient suppression and subsequent recovery 10–25 min after lesion. During this 30-min waiting period, Ringer's lactate solution with or without blood or bicarbonate was infused rapidly when MAP decreased to less than 60 mm Hg or when base excess decreased to less than -5 mmol litre^{-1}, respectively.

All surgical procedures were carried out under ketamine anaesthesia. Preliminary experiments showed that even the lesions down to the pons did not change HSP significantly which, however, decreased when the lesion was made at the middle of the medulla (the fourth procedure). Thus after resection of the midbrain and pons (the third procedure), ketamine infusion was stopped for 30 min to test its effect on HSP in the medulla–spinal cord preparation. In these preparations (midbrain–pons lesioned animals), consciousness was thought to be lost even with elimination of the anaesthetic [8]. Furthermore, ketamine infusion was also stopped for 30 min to examine its effect on the segmental slow positive wave (P2 potential) (fig. 2) after transection of the most caudal part of the medulla (spinalized animals).

Two-way analysis of variance was conducted to identify significant differences in amplitude and latency changes in HSP and segmental spinal cord potentials after each surgical intervention. After this analysis, the least significant difference test for multiple comparison [9] was carried out when significant differences were found. With transection of the most caudal part of the medulla, the amplitudes of both HSP activated by heterosegmental stimulation diminished nearly to zero. For data analysis, these amplitudes were considered less than 1% of control and non-parametric Wilcoxon's signed ranks tests [10] were conducted to calculate statistical significance of differences from control values. $P < 0.05$ was considered significant.

Results

EXPERIMENT I: EFFECTS OF SPINAL CORD TRANSECTION

Neither HP–HSP nor FP–HSP changed significantly when the dorsal one-third of the cord was transected bilaterally at the T8–9 level (table 1, cuts 1 and 2). However, additional hemisection of the dorsal two-thirds of the contralateral cord decreased FP–HSP significantly (table 1, cut 3) with no concomitant significant change in HP–HSP. Bilateral transection of the dorsal two-thirds of the cord (table 1, cut 4) did not lead to further changes in HSP. With complete hemisection of the contralateral cord leaving the ventral one-third of the ipsilateral cord, both FP–HSP and HP–HSP were diminished significantly (table 1, cut 5). Complete transection of the cord caused both HP–HSP and FP–HSP to disappear (table 1, cut 6).

EXPERIMENT II: EFFECTS OF BRAIN RESECTION AND KETAMINE

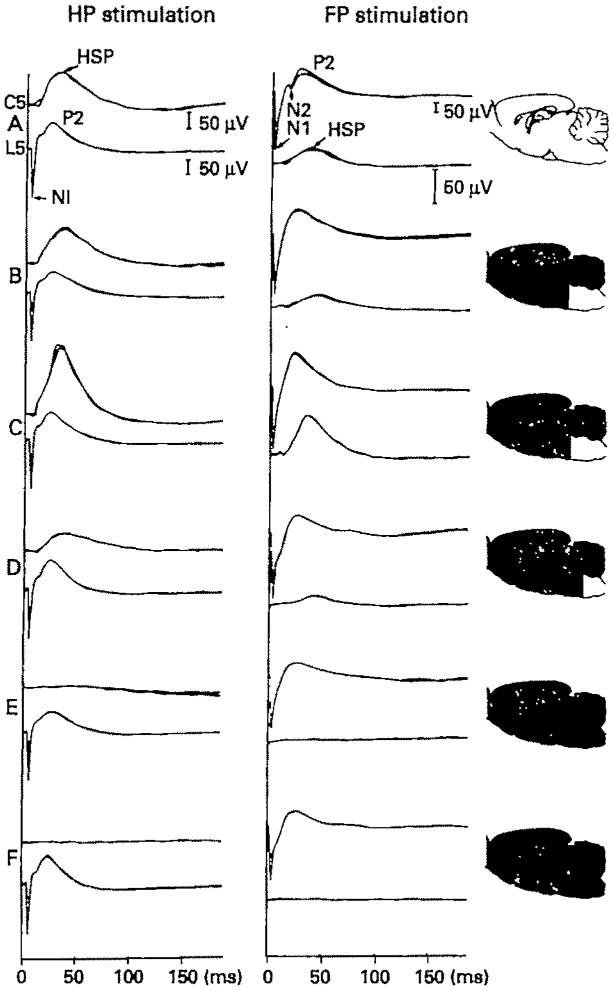


Figure 2 Examples of changes in HSP induced by lesions of the brain at various levels and by ketamine in medulla–spinal cord preparations. A: Before brain lesions during ketamine anaesthesia. HP = Hindpaw; FP = forepaw. Upper sweep, recorded at the C5 level; lower sweep, recorded at the L5 level. N1 = a slow (or sharp) negative wave of the segmental spinal cord potential (segSCP); P2 = a slow positive wave of segSCP; N2 = secondary slow negative wave of segSCP, also recordable in intact animals; HSP = heterosegmental slow positive spinal cord potential. B: HSP following destruction of the cerebral cortex, cerebellum, thalamus with hypothalamus, and midbrain with pons, at the level of AP ± 0, as shown in the right stereotactic drawing, according to Paxinos and Watson [7]. Note that there were no significant changes in HSP, but that the N2 of segSCP disappeared. C: HSP in this medulla–spinal cord preparation 30 min after cessation of ketamine infusion. HSP and P2 of the segSCP were markedly augmented. D: Effects of transecting the medulla oblongata at its middle level (AP -2.5 mm). Both HSP and P2 of segSCP were substantially decreased. E: Effects of transection at the most caudal part of the medulla oblongata at the level of AP -5.75 mm. Note that HSP disappeared and the P2 of segSCP decreased. F: Ketamine infusion was stopped for 30 min in this spinalized preparation. Note that HSP did not reappear, but that the P2 of segSCP was substantially augmented.

Resection of the cerebral cortex and whole cerebellum, and resection of the thalamus with the hypothalamus at the level caudal to the thalamus (Ap + 4.5 mm, see fig. 1) did not affect HSP significantly (table 2, lesions 1 and 2). Resection of the midbrain and pons at the level of AP ± 0 mm (fig. 1) did not decrease the amplitudes of HSP significantly (table 2, lesion 3). At this time, when continuous infusion of ketamine was stopped, HSP were increased significantly. Transection at the middle of the medulla oblongata (fig. 1) decreased HSP significantly (table 2, lesion 4). Transection of the medulla at the most caudal level (AP -5.75) (fig. 1) led to the disappearance of HSP (lesion 5). Even when ketamine infusion was stopped in this prep-

Table 1 Effects of spinal cord transection on HSP and segSCP evoked by hindpaw and forepaw stimulations in ketamine-anaesthetized rats. †Refer to figure 1 for cuts 1–6. HP–HSP = Heterosegmental spinal cord slow positive potential (HSP), recorded from the C5 level, in response to hindpaw (HP) stimulation; HP–segSCP N1 and P2 = slow negative (N1) and positive (P2) waves of the segmental spinal cord potential (segSCP), recorded from the L5 level, in response to HP stimulation; FP–HSP = HSP, recorded from the L5 level, in response to forepaw (FP) stimulation; FP–segSCP N1 and P2 = slow negative (N1) and positive (P2) waves of the segmental spinal cord potential (segSCP), recorded from the C5 level, in response to forepaw stimulation. Values are mean (SD) calculated in nine rats. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, compared with control

Recording level	Spinal cord potentials	Before (%)	Cut 1† (%)	Cut 2 (%)	Cut 3 (%)	Cut 4 (%)	Cut 5 (%)	Cut 6 (%)
Hindpaw stimulation								
C5	HP–HSP	100	110.9 (7.4)	96.2 (19.4)	88.1 (22.8)	85.2 (26.4)	59.4 (24.2)*	0***
L5	HP–segSCP N1	100	101.2 (4.2)	98.8 (4.8)	96.7 (7.8)	95.8 (8.2)	94.7 (10.3)	88.9 (14.9)
	P2	100	118 (16.2)	88.5 (28.7)	84.8 (30.6)	85.3 (34.0)	59.2 (20.7)*	40.5 (21.6)*
Forepaw stimulation								
L5	FP–HSP	100	97.6 (16.1)	87.4 (29.3)	65.6 (18.9)*	67.9 (16.6)*	23.5 (17.8)**	0***
C5	FP–segSCP N1	100	98.8 (4.9)	95.5 (6.9)	96.3 (7.4)	96.1 (8.9)	95.7 (10.1)	92.3 (15.3)
	P2	100	110.5 (15.8)	96.5 (26.0)	95.4 (20.9)	100.1 (23.0)	72.8 (10.9)*	64.2 (22.4)*

aration, HSP did not reappear, but the segmental slow positive potential (P2) showed a significant increase in amplitude compared with that during infusion of ketamine.

Discussion

We have demonstrated that the ascending tract involved in the production of HSP was situated at the ventrolateral quadrant of the spinal cord, whereas the descending tract for the slow potentials was localized partially in the contralateral lateral funiculus and mostly in the bilateral ventrolateral quadrants.

The present study showed also that HSP were not changed significantly by lesions of the cerebral cortex, cerebellum, thalamus, midbrain and pons, but were diminished by transection of the middle part of the medulla and disappeared with transection of the most caudal part of the medulla. The results suggest that the feedback nuclei are situated diffusely in the medulla. Even in the midbrain–pons-eliminated preparation (the medulla–spinal cord preparation), termination of ketamine infusion augmented HSP, suggesting that ketamine produced a depressant effect on HSP also at the level of the central nuclei in the medulla oblongata. Transection of the most caudal part of the medulla led to the disappearance of HSP. Stopping infusion of ketamine in this spinal transection preparation again increased the amplitude of the slow positive component (P2) but not the negative (N1) component of the segmental spinal cord potential (segSCP), suggesting that ketamine also has a depressant effect on HSP and P2 at the level of the spinal cord.

The present method of spinal cord lesion was adopted after several other procedures, including radiofrequency cutting and injection of neurotoxins, were tested. Although these methods were simple, it was difficult to predict accurately the extent of the lesions. The present method of transecting the spinal cord was rather complicated, but may produce an accurately predictable lesion, which was supported by microscopic examination afterwards.

The resection and transection methods of the brain tissue under a microscope and stereotactic apparatus seemed more promising, as these provided an open field to observe the extent of lesion and the complete resection of the brain at a specific level. Blood transfusion was carried out in only three rats in which bleeding exceeded 20 ml kg^{-1} (25–30% of total blood volume). Arterial pressure and heart rate in the other animals were controlled easily by rapid transfusion of Ringer's lactate solution only. Thus this method of brain lesion seemed to be advantageous for defined destruction of brain tissue, provided that bleeding and blood transfusion were controlled properly.

Transection of the spinal cord at the thoracic level (T8–9) has been shown to produce lesions of the ascending tracts for HP–HSP and of the descending tracts for FP–HSP (fig. 1) [1–3, 6]. Bilateral transection of the dorsal one-third of the cord did not affect either FP–HSP or HP–HSP in the present study. This result indicates that the dorsal column system was not responsible for either ascending or descending tracts involved in the production of HSP. Bilateral transection of the dorsal two-thirds of the spinal cord which covers almost all of the dorsal and lateral columns did not affect HP–HSP, and contralateral hemisection of the ventrolateral quadrant and additional total transection decreased significantly and abolished HP–HSP, respectively. These results indicate that the ascending tracts which produce HP–HSP are located bilaterally in the ventrolateral spinal funiculi.

More than two sensory pathways have been shown to be involved in the ventrolateral quadrant; part of the spinothalamic tract projecting to the medial and intralaminar thalamus travelling through the ventromedial funiculus [11], and the spinoreticular system travelling within the ventrolateral quadrant [12–15], although some discrepancies have been reported also [16, 17].

As described in experiment II, HSP were not affected significantly by resection at the level between the thalamus and midbrain, indicating that the rostral part of the spinothalamic tract may not be responsible for the production of HSP. On the other hand, the caudal part of the spinoreticular system which travels through the ventrolateral quadrant [12–15] may be involved in these processes. Fur-

Table 2 Effects of brain lesions on HSP and segSCP evoked by hindpaw and forepaw stimulations in ketamine-anaesthetized and unanaesthetized rats. †Refer to figure 1 for lesions 1–5. HP–HSP = Heterosegmental spinal cord slow positive potential (HSP), recorded from the C5 level, in response to hindpaw (HP) stimulation; HP–segSCP N1 and P2 = slow negative (N1) and positive (P2) waves of the segmental spinal cord potential (segSCP), recorded from the L5 level, in response to HP stimulation; FP–HSP = HSP, recorded from the L5 level, in response to forepaw (FP) stimulation; FP–segSCP N1 and P2 = slow negative (N1) and positive (P2) waves, recorded from the C5 level, in response to forepaw stimulation. Values are mean (SD) calculated in 14 rats. U = unanaesthetized state (30 min after stopping the infusion of ketamine). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, compared with control. ‡$P < 0.05$, ‡‡$P < 0.01$ compared with value during ketamine anaesthesia

Recording level	Spinal cord potentials	Before (%)	Lesion 1† (%)	Lesion 2 (%)	Lesion 3 (%)	Lesion 3U (%)	Lesion 4 (%)	Lesion 5 (%)	Lesion 5U (%)
Hindpaw stimulation									
C5	HP–HSP	100	117.3 (33.4)	122.9 (43.7)	98.9 (43.0)	204.1 (31.4)**††	63.6 (47.2)*	0***	0
L5	HP–segSCP N1	100	101.1 (3.7)	103.4 (4.1)	99.7 (1.9)	105.2 (4.9)	98.1 (3.6)	97.8 (4.5)	102.6 (4.6)
	P2	100	98.0 (10.1)	94.6 (10.6)	95.5 (18.4)	161.2 (11.0)*‡	96.8 (23.9)	89.2 (9.4)*	109.2 (7.1)‡
Forepaw stimulation									
L5	FP–HSP	100	103.1 (20.9)	99.3 (29.8)	80.3 (23.4)	197.9 (24.3)**‡‡	55.2 (27.0)*	0***	0
C5	FP–segSCP N1	100	104.4 (5.1)	102.2 (3.8)	100.2 (3.1)	104.1 (4.8)	99.6 (4.2)	96.8 (5.3)	99.2 (4.0)
	P2	100	97.3 (19.3)	99.6 (16.5)	98.2 (16.9)	170.1 (14.5)*‡	87.1 (17.7)	76.2 (16.1)*	102 (10.1)‡

thermore, the partial decrease in response to lesion of the contralateral ventrolateral quadrant, and complete disappearance of HSP by total transection of the cord indicated that the ascending pathways involved in the production of these slow potentials are partly crossed and partly uncrossed in the ventrolateral quadrant.

Contralateral section of the dorsal two-thirds of the cord decreased significantly FP–HSP, indicating that descending fibres are located partially in this portion. Ipsilateral dorsolateral funiculi may not contain the descending fibres for FP–HSP, as additional section of this portion did not induce further changes in FP–HSP (table 1).

Contralateral hemisection of the ventrolateral cord profoundly affected FP–HSP and total transection of the cord completely eliminated the appearance of FP–HSP. This result indicates that the descending fibres required for production of FP–HSP are situated predominantly in the ventral quadrant of the cord.

Several studies have shown that both the raphe spinal and nucleus reticularis paragigantocellularis (or nucleus reticularis gigantocellularis) spinal tracts travel through bilateral dorsolateral funiculi [18–23]. These tracts have been thought to be important systems for descending inhibitory control of fast pain transmission at the spinal level. In the present study, however, these systems appeared to be involved only partially in the production of HSP, as HSP occurred even with destruction of these two nuclei, and transection of the dorsal one-third of the cord, which includes part of the dorsolateral column, did not affect HSP significantly.

It has been shown also that the pontine and medullary reticulospinal tracts are located in the ventral, ventrolateral and the most ventral portions of the dorsolateral funiculus [24]. Similarly, the rostral part of the medullary raphe nuclei such as the nucleus raphe magnus descends mainly through the dorsolateral funiculus, while the fibres from the caudal parts of the raphe nuclei such as the nuclei raphe pallidus and obscurus are located mainly in the ventral and ventrolateral funiculi [25–27]. Therefore, one or more of these structures could be the candidate which feeds back the impulses to form the descending tract for HSP.

Our data indicate that no brain structures rostral to the medulla (the entire cerebral cortex, thalamus, midbrain, pons and cerebellum) are responsible for producing HSP in ketamine-anaesthetized rats. This does not imply that the central nervous system rostral to the medulla oblongata does not influence HSP. There are four possible explanations for the lack of significant changes in HSP after lesions at or rostral to the pons: (i) ketamine might have substantially suppressed the influences from the higher central nervous system (CNS), resulting in insignificant changes in response to the lesions; (ii) some functional compensation may occur in the CNS, and the lower CNS could take over the function of the higher CNS during the 30-min wait for recovery from traumatic neuronal shock; (iii) the CNS rostral to the medulla may make no contribution to the production of HSP; and (iv) these higher CNS structures may have supplementary influences (facilitatory and inhibitory) on HSP production, whereas the medulla oblongata may be the principal site for feeding back the impulses to the spinal cord to produce HSP.

The fourth mechanism might be the more relevant in view of the results of our present and previous studies [1–5]. In the present study, HSP were augmented markedly by discontinuing the ketamine infusion. This finding supports data from our previous studies that the latencies of HSP are variable in intact rats even during ketamine anaesthesia [2] and divided into two groups in conscious human subjects [5]. Previous studies in cats [26–31] demonstrated that primary afferent depolarization (PAD) could be evoked by stimulation of several CNS structures. These findings support the fourth mechanism proposed above that the principal nuclei involved in HSP production might be situated in the medulla but be influenced by other higher CNS structures.

The substantial decrease in HSP amplitudes observed in middle medulla-lesioned preparations indicates that part of the site responsible for impulse feedback may be situated at or rostral to the middle medulla. Although we could not define a specific nucleus within the medulla oblongata by the present method, it is probable that at least some of the feedback neurones are also located at a rostral region within the medulla.

Additional lesions at the level of the most caudal part of the medulla oblongata abolished HSP completely (table 2). This indicates that another nucleus may be situated within the caudal part of the medulla, and that this part is the site most responsible for the feedback of impulses producing HSP. The caudal part of the medulla does not contain the raphe magnus but includes medullary reticular formations. These structures are known to be tonically influenced by the midbrain reticular formation or periaqueductal grey matter [16, 17, 24–27]. Thus from our present results and those of previous reports on descending inhibitory control of spinal sensory transmission including pain, it is probable that HSP reflect the activities of descending controls activated by heterotopic sensory stimulation.

Recently, it was reported that diffuse noxious inhibitory control (DNIC) was not affected by destruction of PAG, cuneiformis nucleus and parabrachial nucleus by injection of ibotenic acid in the rat, suggesting that the nuclei responsible for DNIC are situated in the caudal part of the medulla. As shown in our previous report [2], however, the neuronal mechanisms may be different between DNIC and HSP, as DNIC is produced only by noxious stimulation [6, 32] while HSP are produced by both non-noxious and noxious stimuli [2–5]. Therefore, we could not document if there is any similarity in the central nuclei producing DNIC and those responsible for the HSP.

Ketamine has been shown to affect cortical and thalamic neuronal activities [33], while having little effect on the midbrain reticular formation [34]. Nevertheless, cessation of ketamine infusion greatly augmented HSP even in the midbrain and pons-lesioned preparations which still contained the medullary reticular formation. Furthermore, slow positive waves (P2) in the segmental spinal cord potential were affected by ketamine in the medulla-lesioned animals (spinalized preparation) (table 2), as observed previously in intact human [35] and rabbit spinal cords [36].

There have been no reports on the effects of ketamine on the activity of the medulla oblongata derived from the influence of higher central nervous structures. The present results have shown that ketamine exhibits depressant effects on FP–HSP and HP–HSP in medulla–spinal cord preparations, and even a slight but significantly depressant effect on the slow P wave (P2) of the segSCP in spinalized preparations, while the negative wave (N1) of the segSCP remained unchanged. The results of the present study indicate that the depressant effects of ketamine on these feedback potentials (FP–HSP and HP–HSP) originated at least in part from the medulla in which the principal nuclei of the HSP are suggested to be localized. The present findings indicate also that segmental PAD, reflected as the P2 of the segmental SCP [1–5], was also suppressed by ketamine in agreement with the results of our previous study in the intact human spinal cord [35]. From this effect of ketamine on the P2 of the segmental SCP, it is also conceivable that the depressant effect of the drug on both FP–HSP and HP–HSP is also in part exerted at the spinal segment level.

Indeed, nociceptive responses [37] and wind-up [38] of dorsal horn neurones have been found to be suppressed by intrathecal pretreatment with the NMDA receptor antagonists, MK-801 [38] and ketamine [39]. On the other hand, our own laboratory [40] has also shown that NMDA antagonists, MK-801 and ketamine, have somewhat different depressant actions depending on NMDA receptor subtypes. Therefore, inhibitory effects of ketamine on the dorsal horn may not be the same in all types of neurones which contribute to production of HSP.

Our previous studies [2–5] have suggested that these slow heterosegmental slow positive potentials, FP–HSP and HP–HSP, reflect the feedback inhibitory potentials, presumably PAD, although more studies should be carried out to establish the relationship between HSP and feedback PAD, and also between rat HSP and human HSP [5]. Thus depressant effects of the drug on these inhibitory potentials may lead to relative excitement in terms of sensory transmission within the cord. Preservation of reflexes and involuntary movements frequently observed during ketamine anaesthesia might be a result at least in part of the depressant effect of the drug on these feedback inhibitory potentials and its segmental inhibitory mechanism.

Acknowledgement

The study was supported in part by a grant-in-aid (No. 04454385) from the Japanese Ministry of Education, Science and Culture.

References

1. Shimoji K, Fujiwara N, Fukuda S, Denda S, Takada T, Maruyama Y. Effects of isoflurane on spinal inhibitory potentials. *Anesthesiology* 1990; **72**: 851–857.
2. Shimoji K, Sato Y, Denda S, Takada T, Fukuda S, Hokari T. Slow positive dorsal cord potentials activated by heterosegmental stimuli. *Electroencephalography and Clinical Neurophysiology* 1992; **85**: 72–80.
3. Shimoji K, Fujiwara N, Denda S, Tomita M, Toyama M, Fukuda S. Effects of pentobarbital on heterosegmentally activated dorsal root depolarization in the rat—Investigation by sucrose-gap technique in vivo. *Anesthesiology* 1992; **76**: 958–966.
4. Shimoji K, Tomita M, Hokari T, Denda S, Tobita T, Baba H, Fukuda S. Human spinal cord potentials recorded from the epidural space. In: Jones SJ, Boyd S, Hetreed M, Smith NJ, eds. *Handbook of Spinal Cord Monitoring, Proceedings of the Fifth International Symposium on Spinal Cord Monitoring*, London, UK, June 2–5, 1992. Dordrecht: Kluwer Academic Publishers, 1994; 21–36.
5. Shimoji K, Tomita M, Tobita T, Baba H, Takada T, Fukuda S, Aida S, Fujiwara N. Erb's point stimulation produces slow positive potentials in the human lumbar spinal cord. *Journal of Clinical Neurophysiology* 1994; **11**: 365–374.
6. Villanueva L, Peschanski M, Calvino B, Le Bars D. Ascending pathways in the spinal cord involved in triggering of diffuse noxious inhibitory controls (DNIC) in the rat. *Journal of Neurophysiology* 1986; **55**: 34–55.
7. Paxinos G, Watson C. *The Rat Brain in Stereotaxic Coordinates*. Sydney: Academic Press, 1982.
8. French JR, Verzeano N, Magoun HW. A neuronal basis of the anesthetic state. *Archives of Neurology and Psychiatry* 1953; **69**: 519–529.
9. Winer BJ. *Statistical Principles and Experimental Design*, 2nd Edn. New York: McGraw Hill Co., 1962; 149–201, 261–308.
10. Ichihara K. *Statistics for Bioscience*. Tokyo: Nankodo, 1991; 50–69.
11. Giesler GJ jr, Menétrey D, Basbaum AI. Differential origins of spinothalamic tract projections to medial and lateral thalamus in the rat. *Journal of Comparative Neurology* 1979; **184**: 107–126.
12. Kerr FWL. The ventral spinothalamic tract and other ascending systems of the ventral funiculus of the spinal cord. *Journal of Comparative Neurology* 1975; **59**: 335–356.
13. Mehler WR. Some neurological species differences—a posteriori. *Annals of the New York Academy of Sciences* 1969; **167**: 424–468.
14. Mehler WR, Feferman ME, Nauta WJH. Ascending axon degeneration following anterolateral cordotomy: An experimental study in monkey. *Brain* 1960; **83**: 718–751.
15. Zemlán FP, Leonard CM, Kow LM, Pfaff DW. Ascending tracts of the lateral columns of the rat spinal cord: A study using the silver impregnation and horseradish peroxidase techniques. *Experimental Neurology* 1978; **62**: 298–334.
16. Lima D. A spinomedullary projection terminating in the dorsal reticular nucleus of the rat. *Neuroscience* 1990; **34**: 577–589.
17. Almeida A, Tavares I, Lima D, Coimbra A. Descending projections from the medullary dorsal reticular nucleus make synaptic contacts with spinal cord lamina I cells projecting to that nucleus: An electron microscopic tracer study in the rat. *Neuroscience* 1993; **55**: 1093–1106.

18: Basbaum AI, Ralston DD, Ralston HJ III. Bulbospinal projections in the primate: A light and electron microscopic study of a pain modulating system. *Journal of Comparative Neurology* 1986; **250**: 311–323.

19. Besson JM, Oliveras JL, Chaouch A, Rivot JP. Role of the raphe nuclei in stimulation producing analgesia. In: Haber B, Gabor S, Issideridis MR, Alivisatos SGA, eds: *Advances in Experimental Medicine and Biology, vol. 133*. New York: Plenum Press, 1981; 153–176.
20. Mayer DJ, Price DD. Central nervous system mechanisms of analgesia. *Pain* 1976; **2**: 379–404.
21. Satoh M, Akaike A, Nakazawa T, Takagi H. Evidence for involvement of separate mechanisms in the production of analgesia by electrical stimulation of the nucleus reticularis paragigantocellularis and nucleus raphe magnus in the rat. *Brain Research* 1980; **194**: 525–529.
22. Willis WD. Control of nociceptive transmission in the spinal cord. In: Ottoson D, ed. *Progress in Sensory Physiology, vol. 3*. New York: Springer, 1982; 1–159.
23. Jones SL, Light AR, Serotoninergic medullary raphespinal projection to the lumbar spinal cord in the rat: A retrograde immunohistochemical study. *Journal of Comparative Neurology* 1992; **322**: 599–610.
24. Kuypers HJGM, Huisman AM. The new anatomy of the descending brain pathways. In: Sjölund B, Björklund A, eds. *Brain Stem Control of Spinal Mechanisms, Fernström Foundation Series, vol. 1*. Amsterdam: Elsevier Biomedical Press, 1982; 29–54.
25. Basbaum AI, Fields HL. The origin of descending pathways in the dorsolateral funiculus of the spinal cord of the cat and rat: Further studies on the anatomy of pain modulation. *Journal of Comparative Neurology* 1979; **187**: 513–532.
26. Martin RF, Haber LH, Willis WD. Primary afferent depolarization of identified cutaneous fibers following stimulation in medial brain stem. *Journal of Neurophysiology* 1979; **42**: 779–790.
27. Walberg F. Paths descending from the brain stem—an overview. In: Sjölund B, Björklund A, eds. *Brain Stem Control of Spinal Mechanisms. Fernström Foundation Series, vol. 1*. Amsterdam: Elsevier Biomedical Press, 1982; 1–27.
28. Andersen P, Eccles JC, Sears TA. Cortically evoked depolarization of primary afferent fibers in the spinal cord. *Journal of Neurophysiology* 1964; **27**: 63–77.
29. Lundberg A, Vyklicky L. Inhibition of transmission to primary afferents by electrical stimulation of the brain stem. *Archives Italiennes de Biologie* 1966; **104**: 86–97.
30. Martin RF, Haber LH, Willis WD. Primary afferent depolarization of identified cutaneous fibers following stimulation in medial brain stem. *Journal of Neurophysiology* 1979; **42**: 779–790.
31. Besson JM, Rivot JP. Spinal interneurones involved in presynaptic controls of supraspinal origin. *Journal of Physiology (London)* 1973; **230**: 235–254.
32. Bouhassira D, Bing Z, Le Bars D. Studies of the brain structures involved in diffuse noxious inhibitory controls: The mesencephalon. *Journal of Neurophysiology* 1990; **64**: 1712–1723.
33. Kayama Y, Iwama K. The EEG, evoked potentials, and single-unit activity during ketamine anesthesia in cats. *Anesthesiology* 1972; **36**: 316–328.
34. Aida S, Fujiwara N, Shimoji K. Differential regional effects of ketamine on spontaneous and glutamate-induced activities of single CNS neurones in rats. *British Journal of Anaesthesia* 1994; **73**: 388–394.
35. Kano T, Shimoji K. The effects of ketamine and neuroleptanalgesia on the evoked electrospinogram and electromyogram in man. *Anesthesiology* 1974; **40**: 241–246.
36. Shimoji K, Matsuki M, Shimizu H. Wave-form characteristics and spatial distribution of evoked spinal electrogram in man. *Journal of Neurosurgery* 1977; **46**: 304–313.
37. Coderre TJ, Melzack R. The contribution of excitatory amino acids to central sensitization and persistent nociception after formalin-induced tissue injury. *Journal of Neuroscience* 1992; **12**: 3665–3670.
38. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on *N*-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain* 1992; **44**: 293–299.
39. Davies SN, Lodge D. Evidence for involvement of *N*-methylaspartate receptors in "wind-up" of class 2 neurones in the dorsal horn of the rat. *Brain Research* 1987; **424**: 402–406.
40. Yamakura T, Mori H, Masaki H, Shimoji K, Mishina M. Different sensitivities of NMDA receptor channel subtypes to non-competitive antagonists. *NeuroReport* 1993; **4**: 687–690.

British Journal of Anaesthesia 1996; **76**: 266–270

Relaxant effect of ketamine and its isomers on histamine-induced contraction of tracheal smooth muscle

K. HIROTA, T. SATO, S. F. RABITO, E. K. ZSIGMOND AND A. MATSUKI

Summary

The mechanism by which racemic ($R(\pm)$) ketamine relaxes airway smooth muscle is unclear and there is no information on the differential effects of ketamine and its isomers. In this study, we have examined the spasmolytic effect of $R(\pm)$ ketamine and its isomers $S(+)$ and $R(-)$ ketamine and the role of intracellular calcium and opioid receptors in $R(\pm)$ ketamine-induced relaxation. The tension of isolated guinea pig tracheal strips was measured isometrically with a force displacement transducer and contraction elicited with histamine 10^{-5} mol litre^{-1}. In histamine-preconstricted strips, the two ketamine isomers (4.5–18.0 × 10^{-4} mol litre^{-1}) produced equipotent relaxation. A subthreshold dose of each isomer of ketamine (10^{-4} mol litre^{-1}) which alone did not relax histamine-induced contraction ($S(+)$, $P < 0.01$; $R(\pm)$, $P < 0.01$; $R(-)$, $P < 0.05$) significantly potentiated adrenaline 1.25–5.0 × 10^{-9} mol litre^{-1}-induced relaxation (potency: $S(+) > R(\pm) > R(-)$). Increase in extracellular Ca^{2+} (1.8–14.4 × 10^{-3} mol litre^{-1}) significantly reduced $R(\pm)$ ketamine-induced relaxation. $S(-)$ Bay K 8644, at concentrations up to 2.0 × 10^{-6} mol litre^{-1}, partially antagonized $R(\pm)$ ketamine-induced relaxation whereas at 10^{-5} mol litre^{-1} or higher it potentiated the response. Naloxone 1.5–6.0 × 10^{-6} mol litre^{-1} did not affect the relaxation caused by $R(\pm)$ ketamine. We conclude that although both ketamine isomers produced equipotent spasmolytic effects on airway smooth muscle precontracted with histamine, they differed in their ability to potentiate the relaxing effect of adrenaline. $S(+)$ ketamine produced the greatest potentiation. Changes in intracellular Ca^{2+} level secondary to a reduction in the L-type Ca^{2+} current may partially mediate the spasmolytic effect of $R(\pm)$ ketamine. (*Br. J. Anaesth.* 1996; **76**: 266–270)

Key words

Anaesthetics i.v., ketamine. Pharmacokinetics, stereoisomers. Airway, muscles. Histamine.

Racemic ($R(\pm)$) ketamine is a potent bronchodilator and has been used for the anaesthetic management of asthmatic patients [1–4]. Although previous reports suggested that the bronchodilator action of $R(\pm)$ ketamine may be caused by increased catecholamine concentrations [5], or by β receptor activation [6], Ca^{2+} channel block [7–9], or both, the precise mechanism of action remains to be determined.

There are many pharmacological differences between optical isomers of ketamine [10–13]. Lundy and colleagues [12] reported that $S(+)$ ketamine can potentiate responses to catecholamines in vascular and anococcygeus muscles to a greater extent than $R(-)$ ketamine. However, the differential effects of ketamine isomers on the response of airway smooth muscle to adrenaline have not yet been reported.

In this study we have determined if ketamine isomers have differential spasmolytic effects on tracheal strips precontracted with histamine and differential potentiating effects on the relaxation produced by adrenaline. In addition, we have studied the role of increased extracellular calcium and opioid receptors on these responses.

Materials and methods

The study was approved by the Animal Care and Use Committee of the University of Illinois at Chicago.

GUINEA PIG TRACHEAL STRIP

Female guinea pigs (300–450 g) were killed with an overdose of sodium pentobarbitone 75 mg kg^{-1} i.p. and section of the abdominal aorta. The trachea was removed, dissected from surrounding tissue and then cut spirally into strips (3 mm × 15 mm) which were mounted in a 10-ml organ bath filled with oxygenated (95% oxygen–5% carbon dioxide) Tyrode's solution at 37 °C. The composition of Tyrode's solution was (mmol litre^{-1}): NaCl 138, KCl 2.7, $MgCl_2$ 1.05, $NaHPO_2$ 0.42, $NaHCO_3$ 11.9, glucose 5.5 and $CaCl_2$ 1.8. Each strip was attached between a fixed point and a force displacement

---

KAZUYOSHI HIROTA*, MD, TETSUMI SATO†, MD, SARA F. RABITO‡, MD, ELEMER K. ZSIGMOND, MD, Department of Anesthesiology, University of Illinois at Chicago, College of Medicine, Chicago, IL 60612, USA. AKITOMO MATSUKI, MD, Department of Anesthesiology, University of Hirosaki School of Medicine, Hirosaki 036, Japan. Accepted for publication: September 6, 1995.

Present addresses:

*University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW.

†Department of Anesthesiology, University of Hirosaki School of Medicine, Hirosaki 036, Japan.

‡Department of Anesthesiology and Pain Management, Cook County Hospital, Chicago, IL 60612, USA.

Correspondence to K.H.

transducer (FT03, Grass Instrument Co., Quincy, MA, USA). After obtaining reproducible contractions to histamine 10^{-5} mol litre^{-1}, experiments were begun. $R(\pm)$, $S(+)$ and $R(-)$ ketamine were tested in random order. Strips were washed for 10 min before each contraction was induced by histamine.

The first experiment was designed to determine the effect of ketamine and its isomers on the tone of tracheal strips precontracted with histamine ($n = 6$). After eliciting maximal contraction to histamine, $R(\pm)$, $S(+)$ or $R(-)$ ketamine was cumulatively added to the organ bath (0.45–1.8 × 10^{-3} mol litre^{-1}). Relaxation was expressed as a percentage (peak contraction, 0 %, fully relaxation, 100 %). The ED_{50} of ketamine (the dose of ketamine that reversed histamine-induced contraction by 50 %) was calculated from the ketamine dose–response curves.

In the second study, we examined the effect of a subthreshold dose of $R(\pm)$ ketamine and its isomers on relaxation induced by adrenaline ($n = 6$). The subthreshold dose of $R(\pm)$ ketamine and its isomers, which alone did not produce relaxation, was determined from the first study. After maximal contraction of each strip was elicited with histamine, 0.9 % saline or $R(\pm)$, $S(+)$ or $R(-)$ ketamine 10^{-4} mol litre^{-1} was administered into the organ bath. Five minutes later, adrenaline was given cumulatively (1.25–5.0 × 10^{-9} mol litre^{-1}) to obtain a dose–response curve to calculate its ED_{50}.

In the third study, we tested if increases in extracellular Ca^{2+} concentration by addition of $CaCl_2$ modified the relaxation produced by $R(\pm)$ ketamine ($n = 6$). The relaxation produced by $R(\pm)$ ketamine 1.8 × 10^{-3} mol litre^{-1} was measured when Ca^{2+} concentrations in the perfusate were increased from 1.8 to 14.4 × 10^{-3} mol litre^{-1}.

In the fourth study ($n = 8$), we tested if the L-type Ca^{2+} channel opener $S(-)$ Bay K 8644 reversed the spasmolytic effect of $R(\pm)$ ketamine. When reproducible contractions to histamine were established, $R(\pm)$ ketamine 9.0 × 10^{-4} mol litre^{-1} was added to the bath followed by cumulative administration of $S(-)$ Bay K 8644 from 2 × 10^{-7} to 10^{-5} mol litre^{-1}.

In the fifth study ($n = 6$), we examined the effect of naloxone on $R(\pm)$ ketamine-induced relaxation. Tracheal strips were precontracted with histamine and the relaxation produced by $R(\pm)$ ketamine 9.0 × 10^{-4} mol litre^{-1} was studied alone and in the presence of naloxone 1.5 × 10^{-6} mol litre^{-1}

DATA ANALYSIS

All data are expressed as mean (SEM). Statistical analysis was by one-way and repeated measures ANOVA followed by Scheffé's *F* test. $P < 0.05$ was considered significant.

DRUGS AND SOLUTIONS

$R(\pm)$ ketamine hydrochloride and histamine hydrochloride were obtained from Sigma Chemical Co. (St Louis, MO, USA), sodium pentobarbitone from Abbott Laboratories (North Chicago, IL, USA) and naloxone from DuPont Pharmaceuticals (Manati, Puerto Rico). $S(+)$, $R(-)$ ketamine hydrochloride was generously donated by Parke-Davis GmbH (Munich, Germany). $S(-)$ Bay K 8644 was obtained from Research Biochemicals Inc. (Natick, MA, USA).

Stock solutions of naloxone and ketamine were prepared in distilled water; $S(-)$ Bay K 8644 was dissolved in methanol (2.8 × 10^{-3} mol litre^{-1}). All stock solutions were stored as aliquots at −20 °C.

Results

EFFECT OF KETAMINE AND ITS ISOMERS ON HISTAMINE-INDUCED CONTRACTIONS

Histamine 10^{-5} mol litre^{-1} increased basal tension by 1.33 (SEM 0.29) g ($n = 6$). After precontraction with histamine, $R(\pm)$ ketamine and its isomers relaxed the tracheal strips in a concentration-dependent manner (fig. 1). There were no significant differences

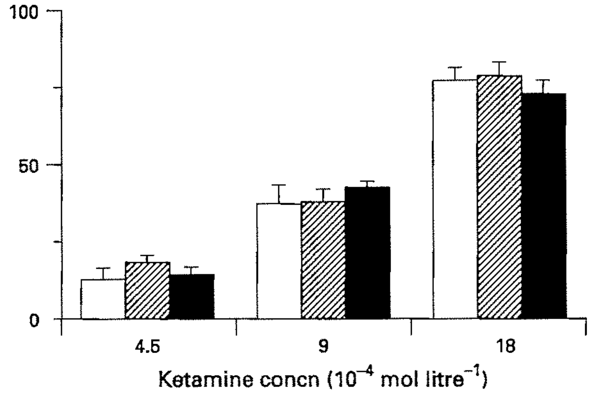


Figure 1 Spasmolytic effect of $R(\pm)$ (▨), $S(+)$ (■) and $R(-)$ (□) ketamine on histamine-induced guinea pig tracheal contractions ($n = 6$). There were no significant differences in the spasmolytic effect between the three forms of ketamine. All values are mean, SEM.

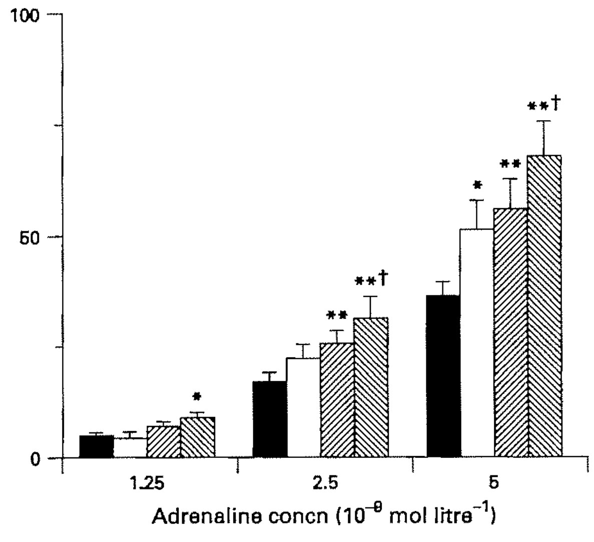


Figure 2 Differential effect of a subthreshold dose (10^{-4} mol litre^{-1}) of each of $R(\pm)$ (▨), $S(+)$ (▧) and $R(-)$ (□) ketamine which potentiated the relaxation of tracheal strips produced by adrenaline. All tracheal strips ($n = 6$) were precontracted with histamine 10^{-5} mol litre^{-1}. $^*P < 0.05$, $^{**}P < 0.01$ compared with adrenaline alone (■); $^\dagger P < 0.05$ compared with adrenaline and $R(-)$ ketamine.

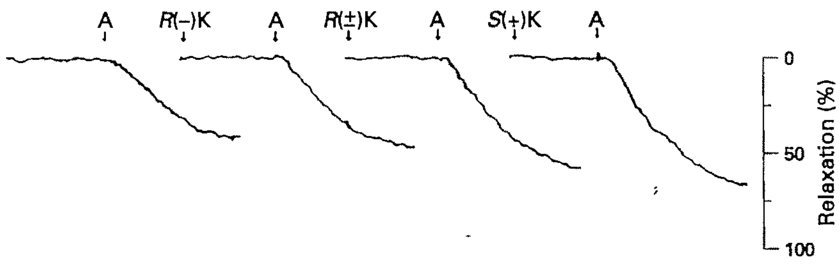


Figure 3 Original recording showing the differential potentiation of a subthreshold dose (10^{-4} mol litre^{-1}) of $R(\pm)$, $S(+)$ and $R(-)$ ketamine (K) on adrenaline (A) 5.0×10^{-9} mol litre^{-1}-induced tracheal relaxation. Each ketamine isomer was given 5 min before the administration of adrenaline. The tracheal strips were precontracted with histamine 10^{-5} min litre^{-1}.

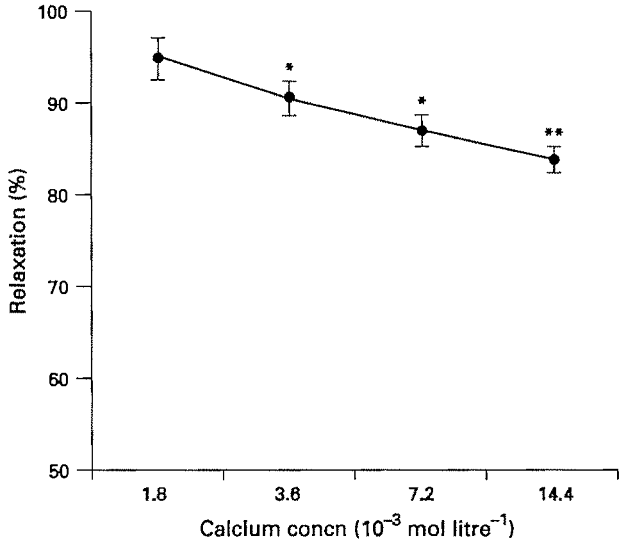


Figure 4 Effect of increasing the extracellular calcium concentration on the relaxation of tracheal strips ($n = 6$) produced by $R(\pm)$ ketamine 1.8×10^{-3} mol litre^{-1}. All tracheal strips were precontracted with histamine 10^{-5} mol litre^{-1}. All values are mean, SEM. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with standard calcium concentration (1.8×10^{-3} mol litre^{-1}) in Tyrode's solution.

between the ED_{50} values of $R(-)$, $R(\pm)$ and $S(+)$ ketamine: 1.14 (0.11), 1.13 (0.09) and 1.09 (0.05) $\times 10^{-3}$ mol litre^{-1}, respectively ($n = 6$). This relaxant effect of $R(\pm)$ ketamine and its isomers was fully reversible after washout.

EFFECT OF A SUBTHRESHOLD DOSE OF KETAMINE AND ITS ISOMERS ON ADRENALINE-INDUCED RELAXATION

Adrenaline relaxed histamine precontracted tracheal strips ($n = 6$) in a concentration-dependent manner (fig. 2). A subthreshold dose (10^{-4} mol litre^{-1}) of $R(-)$, $R(\pm)$ and $S(+)$ ketamine did not change the tension of strips precontracted with histamine (fig. 3). However, the same subthreshold dose significantly reduced the ED_{50} value of adrenaline from 9.4 (1.4) to 5.7 (0.9) $\times 10^{-9}$ mol litre^{-1} after $R(-)$ ketamine ($P < 0.05$); to 4.9 (0.8) $\times 10^{-9}$ mol litre^{-1} after $R(\pm)$ ketamine and to 4.0 (0.8) $\times 10^{-9}$ mol litre^{-1} after $S(+)$ ketamine ($P < 0.01$). $S(+)$ ketamine was more potent than $R(-)$ ketamine at adrenaline 2.5 and 5.0×10^{-9} mol litre^{-1} ($P < 0.05$, fig. 2). The relaxant effect of adrenaline was also fully reversible after washout.

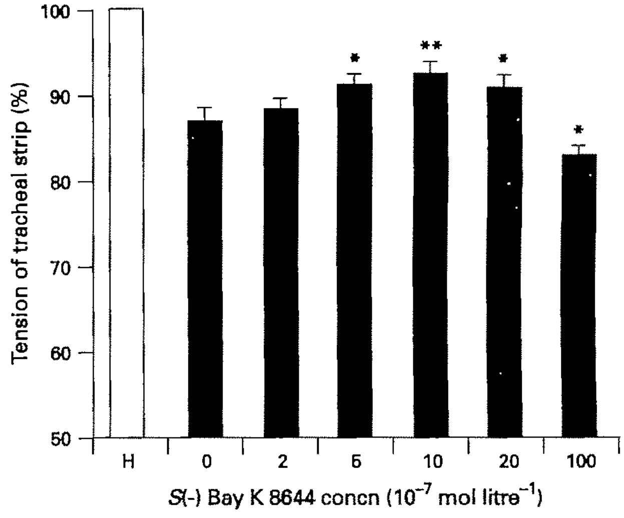


Figure 5 Effect of $S(-)$ Bay K 8644, an L-type calcium channel activator, on the relaxation of tracheal strips ($n = 8$) produced by $R(\pm)$ ketamine 9×10^{-4} mol litre^{-1}. All tracheal strips were precontracted with histamine 10^{-5} mol litre^{-1}. All values are mean, SEM. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with $R(\pm)$ ketamine alone.

EFFECT OF Ca^{2+} CONCENTRATION ON KETAMINE-INDUCED RELAXATION

$R(\pm)$ ketamine 1.8×10^{-3} mol litre^{-1} caused 89.7 (4.6)% relaxation of histamine-induced strip contractions. Increasing the extracellular Ca^{2+} concentration from 1.8 to 14.4×10^{-3} mol litre^{-1} reduced $R(\pm)$ ketamine relaxation by 22.2% (fig. 4, $n = 6$).

EFFECT OF $S(-)$ BAY K 8644, AN L-TYPE Ca^{2+} CHANNEL OPENER, ON KETAMINE-INDUCED RELAXATION

$S(-)$ Bay K 8644 decreased the relaxation of the strips ($n = 8$) produced by $R(\pm)$ ketamine. The maximal effect occurred with $S(-)$ Bay K 8644 10^{-6} mol litre^{-1}. However, $S(-)$ Bay K 8644 10^{-5} mol litre^{-1} potentiated $R(\pm)$ ketamine-induced relaxation (fig. 5).

EFFECT OF NALOXONE ON KETAMINE-INDUCED RELAXATION

$R(\pm)$ ketamine 9.0×10^{-4} mol litre^{-1} significantly reduced histamine-induced contractions from 100 to 64.5 (4.4)% ($n = 6$, $P < 0.01$). However, naloxone added cumulatively (1.5, 3.0 and 6.0×10^{-6} mol litre^{-1} in the bath) did not significantly change relaxation from 64.5 (4.4)% to 64.9 (4.6)%, 67.8 (4.6)% and 62.0 (4.2)%, respectively.

Discussion

$R(\pm)$ ketamine is known to produce bronchodilatation in asthmatic patients who do not respond to conventional therapy [1–4]. Although the mechanism of this spasmolytic effect of $R(\pm)$ ketamine is still unclear, previous studies suggested that Ca^{2+} channel blocking effects [7–9], catecholamine release [5] and/or inhibition of catecholamine uptake [12, 13] may contribute. In addition, Fink and Ngai [11] reported that $R(\pm)$ ketamine inhibited the contractile response of the ileum to electrical stimulation and they suggested that this inhibition by $R(\pm)$ ketamine was mediated partially via opioid receptors.

In the present study, when extracellular Ca^{2+} was increased, the relaxing action of $R(\pm)$ ketamine was reduced in a concentration-dependent manner. Moreover, the L-type Ca^{2+} channel opener, $S(-)$ Bay K 8644, but not naloxone, partially antagonized the relaxation induced by $R(\pm)$ ketamine. Therefore, the spasmolytic effect of $R(\pm)$ ketamine may be caused partially by reduction in L-type Ca^{2+} channel activity. $R(\pm)$ ketamine may produce its relaxant action on airway smooth muscle by inhibition of agonist-induced second messenger synthesis such as inositol 1,4,5-triphosphate [14] or by stimulating Ca^{2+} ATPase to cause Ca^{2+} efflux [15], or both. Further investigation of the action of ketamine at the subcellular level is needed to clearly identify the mechanisms of action, as other modulators such as diacylglycerol, protein kinase C or G proteins may be involved in the relaxing effect of ketamine. We found that $S(-)$ Bay K 8644 10^{-5} mol litre^{-1} potentiated the relaxation produced by $R(\pm)$ ketamine although up to 10^{-6} mol litre^{-1} antagonized the relaxation in a concentration dependent manner. As we dissolved $S(-)$ Bay K 8644 in methanol (0.36% $S(-)$ Bay K 8644 10^{-5} mol litre^{-1}), this may potentiate the effect of ketamine. However, this finding is consistent with previous reports [16–19] that this Ca^{2+} channel opener has a biphasic effect on vascular smooth muscle and cardiac muscle. Wei and colleagues demonstrated that the dual effects of $S(-)$ Bay K 8644 were not caused by involvement of the antagonists isomer, $R(-)$ Bay K 8644 [17]. Another study showed that $S(-)$ Bay K 8644 potentiated or inhibited Ca^{2+} current at polarized and depolarized potentials, respectively [18].

Although the pharmacological differences [10–13] between the ketamine isomers, $S(+)$ and $R(-)$ ketamine, are known, their differential spasmolytic effects on contracted airways have not been reported. Our previous report [9] showed that both isomers equipotently inhibited contraction of guinea pig ileum induced by inflammatory mediators, whereas Fink and Ngai [11] demonstrated that $S(+)$ ketamine was 2–3 times more potent than $R(-)$ ketamine in relaxing guinea pig ileum precontracted by electrical stimulation. In the present study we found that ketamine isomers produced equipotent spasmolytic effects on tracheal strips precontracted with histamine, a result consistent with our previous study on guinea pig ileum [9].

Using rabbit vascular smooth muscle and rat anococcygeus muscle, Lundy, Gverzdys and Frew [20] found that $R(\pm)$ ketamine potentiated the catecholamine response by inhibition of extraneuronal uptake. Using the same muscles [12] they also demonstrated that $S(+)$ ketamine inhibited catecholamine uptake more than $R(-)$ ketamine. In the present study, we found similar results as the subthreshold dose of $R(\pm)$ ketamine and its isomers potentiated adrenalinè-induced relaxation of tracheal strips precontracted by histamine and the potentiating effect of $S(+)$ ketamine was greater than that of $R(-)$ ketamine.

We conclude that the spasmolytic effect of $R(\pm)$ ketamine on contracted airway smooth muscle may result partially from a decrease in Ca^{2+} influx through the L-type Ca^{2+} channel and from inhibition of catecholamine uptake. We suggest that ketamine (especially $S(+)$ ketamine) could be a useful therapeutic agent, in combination with a β_2 agonist, for the treatment of status asthmaticus.

Acknowledgements

We thank Emeritus Professor J. W. R. McIntyre of Edmonton, Canada, for his valuable comments, and Mr Z. Bunevioius and Mr P. Lot for their excellent technical assistance.

References

1. Betts GK, Parkin CE. Use of ketamine in an asthmaticus child. A case report. *Anesthesia and Analgesia* 1971; 50: 514–516.
2. Strub PJ, Hallam PL. Ketamine by continuous infusion in status asthmaticus. *Anaesthesia* 1986; 41: 1017–1019.
3. Rock MJ, DeLaRocha SR, L'Hommedieu CS, Truemper E. Use of ketamine in asthmatic children to treat respiratory failure to conventional therapy. *Critical Care Medicine* 1986; 14: 514–516.
4. Sarma VJ. Use of ketamine in acute severe asthma. *Acta Anaesthesiologica Sandinavica* 1992; 36: 106–107.
5. Kothary SP, Zsigmond EK, Matsuki A. Antagonism of ketamine-induced rise in plasma free-norepinephrine, blood pressure and pulse rate by intravenous diazepam. *Clinical Pharmacology and Therapeutics* 1975; 17, 238.
6. Hirshman CA, Downes H, Farbood A, Bergman NA. Ketamine block of bronchospasm in experimental canine asthmas. *British Journal of Anaesthesia* 1979; 51: 713–718.
7. Baum VC, Tecson ME. Ketamine inhibits transsarcolemmal calcium entry in guinea pig myocardium: direct evidence by single cell voltage clamp. *Anesthesia and Analgesia* 1991; 73: 804–807.
8. Yamazaki M, Ito Y, Shibuya N, Momose Y. Effect of ketamine on voltage-dependent Ca^{2+} currents in single smooth muscle cells from rabbit portal vein. *Pharmacology* 1992; 45: 162–169.
9. Hirota K, Zsigmond EK, Matsuki A, Rabito SF. Ketamine inhibits contractile responses of intestinal smooth muscle by decreasing the influx of calcium through the L-type calcium channel. *Acta Anaesthesiologica Scandinavica* 1995; 39: 759–764.
10. White PF, Way WL, Trevor AJ. Ketamine—Its pharmacology and therapeutic uses. *Anesthesiology* 1982; 56: 119–136.
11. Fink AD, Ngai SH. Opiate receptor mediation of ketamine analgesia. *Anesthesiology* 1982; 56: 291–297.
12. Lundy PM, Lockwood PA, Thompson G, Frew R. Differential effects of ketamine isomers on neuronal and

extraneuronal catecholamine uptake mechanisms. *Anesthesiology* 1986; **64**: 359–363.

13. Hirota K, Zsigmond EK, Matsuki A, Rabito SF. Topical ketamine inhibits albumin extraversion in chemical peritonitis in rats. *Acta Anaesthesiologica Scandinavica* 1995; **39**: 174–178.
14. Kanmmura Y, Kajikuri J, Itoh T, Yoshitake J. Effect of ketamine on contraction and synthesis of inositol, 1,4,5-triphosphate in smooth muscle of the rabbit mesenteric artery. *Anesthesiology* 1993; **79**: 571–579.
15. Abdalla SS, Laravuso RB, Will JA. Mechanisms of the inhibitory effect of ketamine on guinea pig isolated main pulmonary artery. *Anesthesia and Analgesia* 1994; **78**: 17–22.
16. Franckowiak G, Bechem M, Schramm M, Thomas G. The optical isomers of the 1,4-dihydropyridine Bay K 8644 show opposite effects on Ca channels. *European Journal of Pharmacology* 1985; **114**: 223–226.
17. Wei XY, Luchowski EM, Rutledge A, Su CM, Triggle DJ. Pharmacological and radioligand binding analysis of the actions of 1,4-dihydropyridine activator–antagonist pairs in smooth muscle. *Journal of Pharmacology and Experimental Therapeutics* 1986; **239**: 144–153.
18. Kass RS. Voltage-dependent modulation of cardiac calcium channel current by optical isomers of Bay K 8644: implications for channel gating. *Circulation Research* 1986; **61** (Suppl I): I-1–I-5.
19. Wei XY, Rutledge A, Triggle DJ. Voltage-dependent binding of 1,4-dihydropyridine Ca^{2+} channel antagonists and activators in cultured neonatal rat ventricular myocytes. *Molecular Pharmacology* 1989; **35**: 541–552.
20. Lundy PM, Gverzdys S, Frew R. Ketamine: evidence of tissue specific inhibition of neuronal and extraneuronal catecholamine uptake process. *Canadian Journal of Physiology and Pharmacology* 1985; **63**: 298–303.

British Journal of Anaesthesia 1996; **76**: 271–273

Interaction of i.v. anaesthetic agents with 5-HT_3 receptors

B. L. APPADU AND D. G. LAMBERT

Summary

Using N1E-115 neuroblastoma cells as an experimental model, we have examined if four commonly used i.v. anaesthetic induction agents interact with 5-HT_3 receptors. Specifically, we tested the hypothesis that the antiemetic effects of propofol may result from 5-HT_3 receptor antagonism. Binding of tropisetron (a 5-HT_3 selective reference compound), etomidate, ketamine, thiopentone and propofol to 5-HT_3 receptors was assessed by measuring the displacement of [^{3}H]BRL 43694 from whole N1E-115 cells. The rank order potency (K_i) was tropisetron (1.7 (SEM 0.2) nmol litre^{-1}) $\geqslant$ etomidate (83 (4) µmol litre^{-1}) $\geqslant$ ketamine (97 (4) µmol litre^{-1}) > thiopentone (177 (9) µmol litre^{-1}) > propofol (819 (171) µmol litre^{-1}). With the exception of thiopentone these effects were outside the clinical range and suggest that anaesthetic agents are unlikely to interact directly with 5-HT_3 receptors, and that other mechanism(s) must underlie the antiemetic effects of propofol. (*Br. J. Anaesth.* 1995; **76**: 271–273)

Key words

Anaesthetics i.v. Vomiting, nausea. Vomiting, antiemetics. Serotonin (5-hydroxytryptamine). Model, neuroblastoma cells.

Nausea and vomiting are distressing side effects of general anaesthesia. The pathogenesis of postoperative nausea and vomiting is multifactorial [1]. It has been shown that the 5-HT_3 receptor, a member of the ligand-gated, ion channel family [2], is densely located in areas known to be involved in the emetic reflex and could be the key receptor involved in nausea and vomiting [3]. The importance of the 5-HT_3 receptor has been demonstrated in clinical practice where 5-HT_3 antagonists have been used to suppress nausea and vomiting caused by emetic agents [4, 5]. Indeed, selective 5-HT_3 receptor antagonists appear to prevent acute emesis by blocking the initiation of the emetic reflex produced via 5-hydroxytryptamine (5-HT) release from enterochromaffin cells in the gastrointestinal tract in addition to blocking 5-HT_3 receptors in the brain [6].

General anaesthesia with propofol is associated with a decreased incidence of early postoperative nausea and vomiting [7–9]. However, it is unlikely that propofol exerts its antiemetic action via sedation as the duration of its antiemetic effect outlasts its hypnotic effect. It has been suggested recently that propofol has significant direct antiemetic properties [10]. While the exact mechanism of the antiemetic action of propofol is unknown we have recently shown that these effects are unlikely to result from dopamine D_2 receptor antagonism [11]. Using the murine neuroblastoma cell line, N1E-115, as a 5-HT_3 expression system [12], we have examined the effects of four commonly used i.v. anaesthetic induction agents on the binding of [^{3}H]BRL 43694 to 5-HT_3 receptors.

Materials and methods

Mouse neuroblastoma cells of the clone N1E-115 were cultured in Dulbecco's modified Eagle's medium. The growth medium was supplemented with 10% fetal calf serum, with the antibiotics penicillin 100 u. ml^{-1}, streptomycin 100 µg ml^{-1} and Fungizone 2.5 µg ml^{-1}. Cells were cultured to subconfluence in a humidified atmosphere containing 5% carbon dioxide at 37 °C and were passaged every 5–7 days with re-feeding every third day.

Drugs used included: propofol (Zeneca Pharmaceuticals, Macclesfield, UK, lot: 71013/91A) solubilized in dimethylsulphoxide (DMSO); etomidate hydrochloride (Janssen Pharmaceuticals, Bucks, UK); sodium thiopentone (Rhone-Poulenc Rorer, Dagenham, UK, batch 62800) solubilized at 1 mmol litre^{-1} in NaOH 1.0 mol litre^{-1} (when this was added to the binding assay buffer, > 100 × dilution, the pH remained unchanged at 7.4); ketamine hydrochloride (Sigma, Dorset, UK), ICS 205-930 (3-tropanyl-indole-3-carboxylate hydrochloride, tropisetron, Semat, St Albans, UK), [^{3}H]BRL 43694 (specific activity 85.5 Ci mmol^{-1}, NEN Research Products, Herts, UK).

BINDING STUDIES

Binding of i.v. anaesthetic agents to 5-HT_3 receptors was studied using displacement of a fixed concentration (approximately 0.4 nmol litre^{-1}) of the high affinity 5-HT_3 selective antagonist, [^{3}H]BRL

B. L. APPADU, MD, FRCA, D. G. LAMBERT, BSC (HONS), PHD, University Department of Anaesthesia, Leicester Royal Infirmary, Infirmary Close, Leicester LE1 5WW. Accepted for publication: September 6, 1995.

Correspondence to B.L.A.

43694. After removal of growth medium, cells were harvested, washed three times, and resuspended in Krebs–HEPES buffer, pH 7.4, of the following composition (mmol litre^{-1}): Na^+ 143.3, K^+ 4.7, Ca^{2+} 2.5, Mg^{2+} 1.2, Cl^- 125.6, $H_2PO_4^{2-}$ 1.2, SO_4^{2-} 1.2, glucose 11.7 and HEPES 10. Cells were incubated at 37 °C for 60 min in 1-ml volumes of Krebs–HEPES buffer, in the presence of [^{3}H]BRL 43694 and increasing concentrations of displacing drugs (i.v. anaesthetic agents and tropisetron). Bound and free ligand were separated by vacuum filtration onto Whatman GF/B filters using a Brandel cell harvester. Radioactivity retained on the filters was measured by liquid scintillation spectrophotometry. Non-specific binding was defined in the presence of excess tropisetron (10 μmol litre^{-1}) and amounted to $4.8 \pm 1.6\%$ ($n = 34$).

DATA ANALYSIS

The concentration of displacer producing 50% displacement (IC_{50}) was estimated by computer-assisted curve fitting (Graphpad-Prism). IC_{50} values were corrected for the competing mass of [^{3}H]BRL 43694 according to Cheng and Prusoff [13] using a K_D (equilibrium dissociation constant) value for [^{3}H]BRL 43694 of 0.3 nmol litre^{-1} [14] to yield K_i. Statistical comparison of K_i values was made using Student's unpaired t test and considered significant when $P < 0.05$.

Results

Binding of [^{3}H]BRL 43694 was displaced in a dose dependent manner by the $5HT_3$ selective reference compound, tropisetron. The calculated affinity (1.7 nmol litre) was consistent with previous reports [15–17]. In addition, there was a dose-dependent displacement of [^{3}H]BRL 43694 by the four anaesthetic agents tested. The curves shown in figure 1 and analysed in table 1 are based on maximum displacement of 100%, although this was not achieved experimentally. The rank order potency was etomidate ≥ ketamine > thiopentone > propofol. DMSO, the vehicle for propofol, produced < 5% displacement of [^{3}H]BRL 43694 at the highest concentration (300 μmol litre^{-1}) of propofol only. With the exception of thiopentone, these effects fell outside the clinically relevant serum concentrations [18–21].

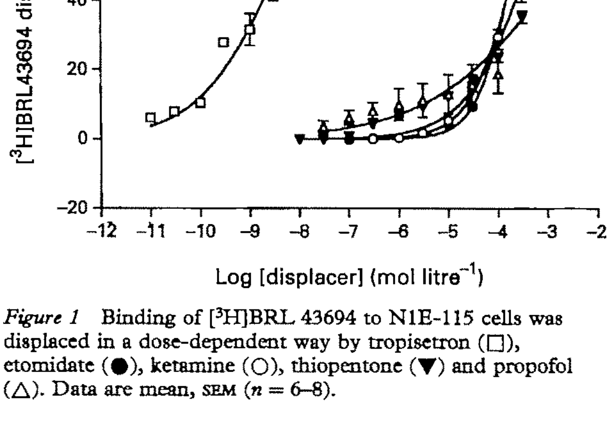


Figure 1 Binding of [^{3}H]BRL 43694 to N1E-115 cells was displaced in a dose-dependent way by tropisetron (□), etomidate (●), ketamine (○), thiopentone (▼) and propofol (△). Data are mean, SEM (n = 6–8).

Table 1 K_i values (mean (SEM)) for tropisetron and the four i.v. anaesthetic agents. Data are derived from the curves in figure 1. ‡ Peak at induction, not corrected for protein binding. Subhypnotic doses would be lower. * $P < 0.05$, less potent than ketamine and etomidate; † $P < 0.05$, less potent than thiopentone, ketamine and etomidate

	n	K_i	Clinical concn‡ (μmol litre^{-1})
Tropisetron	6	1.7 (0.2) nmol litre^{-1}	Not available
Etomidate	6	83.2 (3.8) μmol litre^{-1}	10 [18]
Ketamine	6	96.9 (3.5) μmol litre^{-1}	20 [19]
Thiopentone	6	177.3 (9.4) μmol litre^{-1}*	380 [20]
Propofol	8	819.0 (171.3) μmol litre^{-1}†	35 [21]

Discussion

We have demonstrated that four commonly used i.v. anaesthetic induction agents exert little direct effect on endogenous 5-HT_3 receptors in a cultured neuronal cell line, N1E-115. There was some overlap with the K_i for thiopentone and the observed peak serum concentration. However, these studies do not enable predictions to be made as to whether thiopentone is acting as an agonist (emetic) or antagonist (antiemetic). More importantly, our studies suggested that the reported antiemetic action of propofol [7–9] is unlikely to be caused by 5-HT_3 receptor block as the K_i values of propofol exceeded the peak plasma and brain [22] anaesthetic concentrations. In addition, the K_i was approximately 25-fold greater than plasma propofol concentrations at subhypnotic doses, where a significant antiemetic action can be demonstrated [7–9]. However, it should be noted that there may be interspecies variation in the 5-HT_3 receptor and consequently K_i values in mouse cells may not be a true reflection of those in humans.

Our results are at variance with the findings of a recent study of the action of i.v. anaesthetics with the 5-HT_3 receptor by Barann and colleagues [23], who found that i.v. anaesthetics inhibited 5-HT-induced flux of ^{14}C-guanidinium through the cation channel of the 5-HT_3 receptor. The rank order of potency in their study was propofol > etomidate > thiopentone > ketamine (in our study we found propofol the least potent). This functional block of the 5-HT_3 receptor by anaesthetic drugs may result from channel block rather than receptor antagonism, but suggests that direct 5-HT_3 receptor antagonism may not be *the only way* to reduce emesis, in that "downstream" functional block may also be important. As the inhibition of ^{14}C-guanidinium influx [23] was non-competitive, this modifies the general conclusions of our study. While there does not appear to be 5-HT$_3$ receptor block, channel inhibition by anaesthetic agents appears to be a viable and potent [23] mechanism for producing antiemesis. However, thiopentone and etomidate do not appear to exert significant antiemetic action but still reduce 5-HT$_3$ function at clinically relevant doses.

References

1. Lerman J. Surgical and patient factors involved in post-operative nausea and vomiting. *British Journal of Anaesthesia* 1992; **69** (Suppl. 1): 24S–32S.
2. Maricq AV, Peterson AS, Brake AJ, Myers RM, Julius D. Primary structure and functional expression of the 5-HT$_3$ receptor, a serotonin-gated ion channel. *Science* 1991; **254**: 432–437.
3. Kilpatrick GJ, Jones BJ, Tyers MB. Identification and distribution of 5-HT$_3$ receptors in rat brain using radioligand binding. *Nature (London)* 1987; **330**: 746–748.
4. Miner WD, Sanger GJ. Inhibition of cisplatin-induced vomiting by 5-hydroxytryptamine m-receptor antagonism. *British Journal of Pharmacology* 1986; **88**: 497–499.
5. Leeser J, Lip H. Prevention of postoperative nausea and vomiting using ondansetron, a new selective, 5-HT$_3$ antagonist. *Anesthesia and Analgesia* 1991; **72**: 751–755.
6. Carpenter DO. Neural mechanisms in emesis. *Canadian Journal of Physiology and Pharmacology* 1990; **68**: 230–236.
7. McCollum JSC, Milligan KR, Dundee JW. The antiemetic action of propofol. *Anaesthesia* 1988; **43**: 239–240.
8. Raftery S, Sherry E. Total intravenous anaesthesia with propofol and alfentanil protects against nausea and vomiting. *Canadian Journal of Anaesthesia* 1992; **39**: 37–40.
9. Weir PM, Munro HM, Reynolds PI, Lewis IH, Wilton NCT. Propofol infusion and the incidence of emesis in pediatric outpatient strabismus surgery. *Anesthesia and Analgesia* 1993; **76**: 760–764.
10. Borgeat A, Wider-Smith OHG, Saiah M, Rifat K. Sub-hypnotic doses of propofol possess direct antiemetic properties. *Anesthesia and Analgesia* 1992; **74**: 539–541.
11. Appadu BL, Strange PG, Lambert DG. Does propofol interact with D$_2$ dopamine receptors? *Anesthesia and Analgesia* 1994; **79**: 1191–1192.
12. Neijt HC, Te Duits IJ, Vijverberg HPM. Pharmacological characterization of serotonin 5-HT$_3$ receptor-mediated electrical response in cultured mouse neuroblastoma cells. *Neuropharmacology* 1988; **27**: 301–307.
13. Cheng YC, Prusoff WH. Relationship between the inhibitor constant (K$_i$) and the concentration of inhibitor which causes 50% inhibition (IC$_{50}$) of an enzymatic reaction. *Biochemical Pharmacology* 1973; **22**: 3099–3108.
14. Nelson DR, Thomas DR. [^{3}H]-BRL 43694 (granisetron), a specific ligand for 5-HT$_3$ binding sites in rat brain cortical membranes. *Biochemical Pharmacology* 1989; **38**: 1693–1695.
15. Hoyer D, Neijt HC. Identification of serotonin 5-HT$_3$ recognition sites in membranes of N1E-115 neuroblastoma cells by radioligand binding. *Molecular Pharmacology* 1988; **33**: 303–309.
16. Lummis SCR, Kilpatrick GJ, Martin IL. Characterization of 5-HT receptors in intact N1E-115 neuroblastoma cells. *European Journal of Pharmacology (Molecular Pharmacology section)* 1990; **189**: 223–227.
17. Kooyman AR, Van Hooft JA, Vanderheijden PML, Vijverberg HPM. Competitive and non-competitive effects of 5-hydroxyindole on 5-HT$_3$ receptors in N1E-115 neuroblastoma cells. *British Journal of Pharmacology* 1994; **112**: 541–546.
18. Van Hamme MJ, Ghoneim MM, Ambre JJ. Pharmacokinetics of etomidate, a new intravenous anesthetic. *Anesthesiology* 1978; **49**: 274–277.
19. White PF, Ham J, Way WL, Trevor AJ. Pharmacology of ketamine isomers in surgical patients. *Anesthesiology* 1990; **52**: 231–239.
20. Burch PG, Stanski DR. The role of metabolism and protein binding in thiopental anesthesia. *Anesthesiology* 1983; **58**: 146–152.
21. Shafer A, Doze VA, Shafer SL, White PF. Pharmacokinetics and pharmacodynamics of propofol infusion during general anesthesia. *Anesthesiology* 1988; **69**: 348–356.
22. Shyr MH, Tsai TH, Tan PPC, Chen CF, Chan SH. Concentration and regional distribution of propofol in brain and spinal-cord during propofol anesthesia in rats. *Neuroscience Letters* 1995; **184**: 212–215.
23. Barann M, Göthert M, Fink K, Bönsich H. Inhibition by anaesthetics of ^{14}C-guanidinium flux through the voltage-gated sodium channel and the cation channel of the 5-HT$_3$ receptor of N1E-115 neuroblastoma cells. *Naunyn-Schmiedebergs Archives of Pharmacology* 1993; **347**: 125–132.

British Journal of Anaesthesia 1996; **76**: 274–277

Effects of morphine on human nasal cilia beat frequency *in vitro*†

D. A. SELWYN, J. H. RAPHAEL, D. G. LAMBERT AND J. A. LANGTON

Summary

Using human nasal cytological brushings, we have investigated the effects of morphine on ciliary function by measurement of cilia beat frequency *in vitro*, and we have also determined opioid receptor binding in these specimens. We obtained ciliated samples from seven volunteers, and measured cilia beat frequency using the transmitted light technique during exposure to morphine 10 μmol litre^{-1} for 4 h. Mean cilia beat frequency of the samples exposed to morphine was 11.1 (95% confidence interval 10.9–11.5) Hz and that of the controls 11.3 (11.1–11.7) Hz. There was no significant effect of morphine on human cilia beat frequency *in vitro* (MANOVA for repeated measures and nested, $F = 0.61$, $P = 0.66$). In a separate study, we obtained nasal brushings from 20 patients and measured the binding of the opioid antagonist tritiated diprenorphine([^{3}H]DPN). Mean disintegrations per minute (dpm) for total and non-specific binding were 9036 (8105–9967) dpm and 9130 (8054–10206) dpm, respectively. These values did not differ significantly (paired *t* test, $t = 0.22$, $P = 0.83$). We conclude that morphine had no effect on cilia beat frequency *in vitro* and we were unable to demonstrate any significant numbers of opioid receptors on nasal ciliated epithelium. (*Br. J. Anaesth.* 1996; **76**: 274–277)

Key words

Lung, trachea. Analgesics opioid, morphine. Receptors, opioid.

Opioids are potent analgesics that form the mainstay of perioperative pain relief and are widely used as sedatives in the intensive care unit. A variety of such agents, both natural and synthetic, are available, but one of the commonest agents used in these circumstances is morphine. Several studies have reported a depressant effect of morphine on respiratory mucus transport which is one of the most important defences against respiratory tract infections.

In a study of anaesthetized cats in which barium sulphate was insufflated into the lungs, Van Dongen and Leusink found that the administration of morphine 0.5 mg kg^{-1} s.c. delayed the clearance of the radiological marker by a factor of 2–3 times, a distal airways phenomenon [1]. Using a radioactive droplet technique, Forbes and Horrigan measured mucociliary flow in the trachea in dogs. Compared with those respiratory tracts ventilated with 40% nitrous oxide in air, the addition of morphine 6 mg kg^{-1} i.v. reduced mucus transport rates to 70% of controls. This reduction was similar to that found with 1.2 MAC of halothane [2].

Chest infections are one of the commonest forms of serious morbidity after surgery, with an incidence of 6–21% [3–6]. Chest infection is also common in intensive care patients and may develop in about one-third of patients in the ITU [7]. As mucociliary clearance is an important respiratory defence mechanism, its impairment by morphine may have relevance in the postoperative period and in the ITU.

The rate of mucus transport depends on the volume and physical properties of mucus and on the function of the cilia; however, the mechanism by which morphine reduces mucus transport rate has not been elucidated. There are two studies that have investigated the effects of opioids on cilia and have shown a reduction in beat frequency [8, 9]. These studies have been *in vivo* investigations complicated by the administration of other drugs. We have investigated the effects of morphine on human respiratory ciliary function by measuring cilia beat frequency and opioid receptor density using nasal epithelial cell brushings *in vitro*.

Materials and methods

EFFECTS OF MORPHINE ON CILIA BEAT FREQUENCY

After obtaining Ethics Committee approval and informed consent, we obtained samples of ciliated epithelium from seven (six female) non-smoking healthy patients, mean age 40.3 (range 21–56) yr. None of the patients was taking any medication or had an upper respiratory tract infection within the previous 4 weeks. No premedication was given. The samples were acquired by passing a bronchoscopy brush over the inferior nasal turbinates after induction of anaesthesia with propofol 2–3 mg kg^{-1}. The tissue was removed from the brush by agitation in Hanks buffered salt solution (HBSS).

D. A. SELWYN, FRCA, J. H. RAPHAEL, FRCA, D. G. LAMBERT, PHD, J. A. LANGTON, MD, FRCA, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. Accepted for publication: September 22, 1995.

Correspondence to J.H.R.

†A preliminary report of part of this study was presented at the Anaesthetic Research Society, London Meeting, November 11–12, 1994 (*British Journal of Anaesthesia* 1995; 74: 484P–485P).

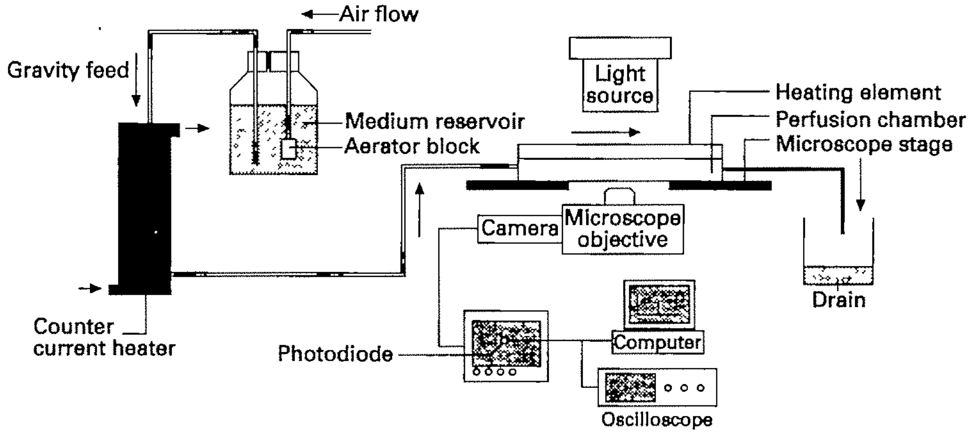


Figure 1 Schematic diagram of the cilia perfusion system.

The ciliated samples from each individual were placed between the coverslips of paired perfusion chambers as described previously [10] (fig. 1). Each chamber was perfused from a separate delivery bottle of HBSS into the entry port of the chamber and out from its exit port into a collecting beaker. HBSS was aerated at 1000 ml min^{-1} and perfused the chambers under the effect of gravity at a constant rate of 0.5 ml min^{-1}. Morphine was added to one delivery bottle in a concentration of 10 μmol litre^{-1}. The observer did not know which chamber received morphine as the delivery tubes from the bottles to the chambers were wound around one another within a countercurrent water jacket. The bottles of HBSS were immersed in a water bath at 37 ($\pm$0.1) °C that also surrounded the countercurrent heat exchanger around the delivery tubing. The perfusion chambers were maintained at 37 °C by means of a thermostatically controlled heating element on the underside of the chamber.

To confirm that morphine was reaching the chamber from the delivery bottle in an adequate concentration, we sampled the perfusate downstream of the perfusion chamber and measured morphine concentrations by high performance liquid chromatography (HPLC). We used an 18C column, 25 cm in length, with phosphate buffer at pH 2 running at 1 ml min^{-1} and electrochemical detection with a carbon electrode. The lower limit of this assay for morphine was of the order of 1 ng ml^{-1} [11].

For measurement of cilia beat frequency we used a photometric method as described previously [10]. This involved detection of ciliary movements using a differential interference contrast microscope (Nikon Diaphot 200) and transmission of the image to a monitoring screen. Cilia beat frequency is determined by their interference with the light reaching a pinhead photodetector attached to the monitoring screen. Voltage changes across the photodetector were amplified to provide a signal on an oscilloscope greater than 0.2 V and low-pass filtered with a cutoff above 25 Hz. Ciliary movements were recorded for a period of 15 s and the voltage changes across the photodetector were digitized and mathematically processed to give a power spectrum. The signals produced by the beating cilia over a 15-s period were divided into three sequential 5-s intervals for analysis. We computed the peak frequency of one power spectrum obtained by calculating the mean of the power spectra for each epoch. A mean of the dominant frequency of each of the three 5-s epochs was then computed. Although shortening the capture time reduced the resolution of measurement to 0.2 Hz, this was not a limiting factor within the experimental conditions used and it increased the confidence interval of the calculated mean beat frequency. The microscope was mounted on a concrete block to minimize interference produced by extraneous vibration.

When the chambers had equilibrated to 37 °C as indicated by the temperature plate on the chamber base, recordings of cilia beat frequency were commenced. Acceptable ciliated edges for measurement were deemed to be those free of mucus, at least 60 μm long and not part of single cells. Readings were taken from both chambers before the addition of morphine and 1, 2, 3 and 4 h after morphine had been added to one chamber by analysing as many acceptable ciliated edges as possible from a minimum of six to a maximum of 12 from each chamber in each defined time band.

At the end of each experiment, it was determined which chamber had received morphine and the samples were discarded. The data approximated to a normal distribution and were analysed by MANOVA for repeated measures and nested using polynomial contrasts, with significance taken at $P <$ 0.05 (SPSS for windows v 5.01).

BINDING OF [^{3}H]DPN TO HUMAN NASAL CILIATED EPITHELIAL CELL MEMBRANES

To determine if opioid receptors were present on cilia, we measured the binding of tritiated diprenorphine, [^{3}H]DPN, a non-selective opioid antagonist, to ciliated epithelial cell membranes [12].

After obtaining Ethics Committee approval and informed patient consent, we collected nasal ciliated epithelial cells on two separate occasions by the methods described earlier. This involved passing a bronchoscopy brush over the inferior nasal turbinates of 10 healthy patients on each occasion after they had received an anaesthetic induction dose of propofol 2–3.3 mg kg^{-1}. The samples were removed from the brushes by agitation in M199. The tissue was washed in Tris HCl 50 mmol litre^{-1}–NaCl 100 mmol litre^{-1}, buffered to pH 7.4. The tissue was homogenized using three 15-s bursts with a tissue tearer and then centrifuged at 13500 rpm for 10 min at 40 °C. This process of homogenization and centrifugation was repeated three times and the cell membranes were then resuspended in 2 ml of the above buffer. Binding studies were performed in 1-ml assay volumes of Tris HCl for 60 min at 37 °C containing a saturating concentration of [^{3}H]DPN 3.7–4.3 nmol litre^{-1}. Non-specific binding was defined in the presence of excess naloxone 10 µmol litre^{-1}.

Bound and free radioactivity were separated by rapid vacuum filtration using a Brandel cell harvester onto Whatman GF/B filters and washed with three 4-ml aliquots of ice cold buffer. After overnight extraction, bound radioactivity was measured by scintillation spectroscopy with Optiphase-X (LKB Wallac) as a scintillant.

Results

We made a total of 739 measurements of cilia beat frequency: 374 from the cilia exposed to morphine and 365 from the controls. Mean cilia beat frequency of the samples exposed to morphine was 11.1 (95% confidence interval 10.9–11.5) Hz and that of the controls 11.3 (11.1–11.7) Hz (MANOVA for repeated measures and nested, $F = 0.61$, $P = 0.66$) (fig. 2).

Mean total and non-specific binding at DPN 3.7–4.3 nmol litre^{-1} were 9036 (8105–9967) dpm and 9130 (8054–10206) dpm, respectively (table 1). These values were not significantly different, indicating no specific binding (paired t test, $t = 0.22$, $P = 0.83$).

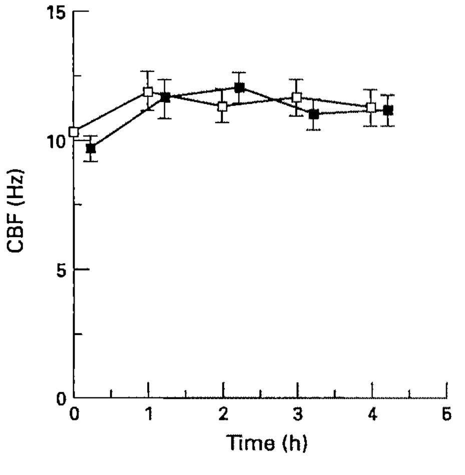


Figure 2 Effects of morphine (■) and control (□) on cilia beat frequency (CBF) (mean (95% confidence interval)).

Discussion

We did not find a significant effect of morphine on cilia beat frequency measured *in vitro* with human nasal cytological samples and were unable to demonstrate the presence of opioid receptors in this tissue.

The variability in the measurements of cilia beat frequency was large. There was greater variability of within-sample measurements than between-sample measurements because of differences in cilia beat frequency between different ciliated edges. Taking n to be the number of ciliated edges measured at any one time, we have computed a *post hoc* power of 80% to detect differences greater than 2 Hz at the 5% level of significance. This represents a change in cilia beat frequency of less than 20%; however, because of the non-linear relationship between cilia beat frequency and mucus transport rate [13], it is possible that small changes in cilia beat frequency may be associated with large changes in mucus transport rate. We elected to investigate binding of opioids to ciliated tissue to substantiate our negative finding.

The concentration we investigated, 10 µmol litre^{-1}, is at the upper limit of the range found in clinical practice, that is the plasma concentration found in patients receiving up to 1500 mg of morphine per day for the treatment of cancer pain [14].

We found an initial small increase in cilia beat frequency in both the control and treatment groups. This may have resulted from the effects of sampling or a delay in the chamber medium equilibrating with temperature.

Studies comparing cilia from the nose with those further down the respiratory tract have found a similar beat frequency [15] and the effects of other drugs on nasal and tracheal tissue are similar [16, 17], suggesting that nasal samples are representative of cilia further down the bronchial tree; however, it is possible that they may not have a similar response to morphine.

There are few comparable studies on the effects of morphine on cilia beat frequency. Rutland, Griffen and Cole measured cilia beat frequency of human nasal brushings with a photometric technique after premedication with the opioid papaveretum and atropine [8]. They found that mean cilia beat frequency in premedicated patients was 11.4 (SD

Table 1 Binding of [^{3}H]DPN to human nasal ciliated cell membranes. No specific binding was detected. Data in each experiment are mean (95% confidence interval) for six determinations of total and NSB in each experiment. Mean values are 12 determinations

		DPN binding (dpm)	
	No. of patients	Total	NSB
Experiment 1	10	8235 (7465–9004)	8106 (6124–10090)
Experiment 2	10	9837 (8129–11544)	10153 (9658–10649)
Mean	20	9036 (8105–9967)	9130 (8054–10206)

1.4) Hz compared with 13.1 (1.9) Hz in a group of awake and unpremedicated controls; this difference was statistically significant ($P < 0.001$). Roth and coworkers used a similar method to directly measure cilia beat frequency *in vitro* from nasal brushings and compared results from the same patients before and after administration of an opioid-containing premedication [9]. The patients received a mixture of morphine 5–10 mg i.v., atropine 1 mg i.m. and 2% lignocaine 2–3 ml applied topically to the nose. The authors found a small but significant reduction in ciliary beat frequency after medication from a mean of 12.2–11.0 Hz. In both of these studies, the addition of other drugs limits interpretation. Although low doses of lignocaine do not affect ciliary beat frequency *in vitro* [18], 2% lignocaine has been shown to cause ciliostasis in human nasal biopsy specimens [19]. Atropine is known to inhibit mucus transport rates in humans [20]; however, this appears to be caused by inhibition of mucus secretion and there is little direct evidence for a depressant effect on the cilia [21].

Another explanation for the conflict in our results with those described above may relate to differences in methods. We elected to measure cilia beat frequency from all visible edges whereas other workers appear to have measured the fastest beating ciliated edges. Consequently, the variation in our measurements was large; however, selection of certain ciliated edges, as used by other workers, introduces a bias that we avoided.

Using [^{3}H]DPN at a concentration that would occupy all opioid receptors, we failed to demonstrate any specific binding (receptors) on nasal ciliated epithelial cell membranes. This concurs with our *in vitro* findings of the absence of effects of morphine on cilia beat frequency.

The mechanisms by which morphine reduces mucociliary transport *in vivo* remain to be elucidated. They may be related to effects on mucus or to *in vivo* effects on the cilia. Rogers and Barnes showed that morphine reduced mucus secretion stimulated by capsaicin in bronchitic patients [22]. One could speculate that during anaesthesia which involves procedures and agents that are irritant to the airways, morphine might similarly inhibit mucus secretion. Reduction in the secretion of mucus and its subsequent movement might alter its physical properties which would affect the function of the cilia, an effect that would not be observed with mucus-free *in vitro* preparations.

Although there is no evidence for neural control of ciliary function in humans, there are free nerve endings adjacent to the basement membrane [23]. An alternative hypothesis is that morphine may have an effect on cilia *in vivo* because of effects on neural connections which are absent from *in vitro* preparations.

References

1. Van Dongen K, Leusink H. The action of opium-alkaloids and expectorants on the ciliary movements in the air passages. *Archives Internationales de Pharmacodynamie et de Therapie* 1953; **93**: 261–276.
2. Forbes AR, Horrigan RW. Mucociliary flow in the trachea during anesthesia with enflurane, ether, nitrous oxide, and morphine. *Anesthesiology* 1977; **46**: 319–321.
3. King DS. Postoperative pulmonary complications. *Surgery, Gynecology and Obstetrics* 1933; **56**: 43–50.
4. Wightman JAK. A prospective study of the incidence of postoperative pulmonary complications. *British Journal of Surgery* 1968; **58**: 85–91.
5. Garibaldi RA, Britt MR, Coleman ML, Reading JC, Pace NL. Risk factors for postoperative pneumonia. *American Journal of Medicine* 1981; **70**: 677–680.
6. Dilworth JP, White RJ. Postoperative chest infection after upper abdominal surgery: an important problem for smokers. *Respiratory Medicine* 1992; **86**: 205–210.
7. Riuz-Santana S, Jimenez AG, Esteban A, Guerra L, Alvarez B, Corcia S, Gudin J, Martinez A, Quintana E, Armengol S, Gregori J, Arenzana A, Rosada L, Sanmartin A. ITU pneumonias: a multi-institutional study. *Critical Care Medicine* 1987; **15**: 930–932.
8. Rutland J, Griffen W, Cole PJ. An in vitro model for studying the effects of pharmacological agents on human ciliary beat frequency: effects of lignocaine. *British Journal of Clinical Pharmacology* 1982; **13**: 679–683.
9. Roth Y, Aharonson EF, Teichtahl H, Baum GL, Priel Z, Modan M. Human in vitro nasal and tracheal ciliary beat frequencies: comparison of sampling sites, combined effect of medication, and demographic relationships. *Annals of Otology and Laryngology* 1991; **100**: 378–384.
10. Selwyn DA, Gyi A, Key A, Mottram SD, Langton JA. A perfusion system for the in vitro measurement of human respiratory cilia beat frequency. *British Journal of Anaesthesia* 1994; **73**: 269.
11. Venn RF, Michalkiewicz A. Fast reliable assay for morphine and its metabolites using high performance liquid chromatography and native fluorescence detection. *Journal of Chromatography* 1990; **525**: 378–388.
12. Lambert DG, Atcheson R, Hirst RA, Rowbotham DJ. Effects of morphine and its metabolites on opiate receptor binding, cAMP formation and [3H]noradrenaline release from SH-SY5Y cells. *Biochemical Pharmacology* 1993; **46**: 1145–1150.
13. Duchateau GSMJE, Graamans K, Zuidema J, Merkus FWHM. Correlation between nasal cilia beat frequency and mucus transport rate in volunteers. *Laryngoscope* 1985; **95**: 854–859.
14. Goucke CR, Hackett LP, Ilett KF. Concentrations of morphine, morphine-6-glucuronide and morphine-3-glucuronide in serum and cerebrospinal fluid following morphine administration to patients with morphine-resistant pain. *Pain* 1994; **56**: 145–149.
15. Low PP, Luk CK, Dulfano MJ, Finch PJP. Ciliary beat frequency of human respiratory tract by different sampling techniques. *American Review of Respiratory Disease* 1984; **130**: 497–498.
16. Gyi A, O'Callaghan C, Langton JA. A pilot study of the effect of halothane on human ciliary beat frequency *in vitro*. *British Journal of Anaesthesia* 1993; **71**: 757P–758P.
17. Lee KS, Park SS. Effect of halothane, enflurane and nitrous oxide on tracheal ciliary activity in vitro. *Anesthesia and Analgesia* 1980; **59**: 426–430.
18. Rutland J, Griffen W, Cole P. Nasal brushing and measurement of ciliary beat frequency. *Chest* 1981; **80**: 865–867.
19. Ingels KAJO, Nijziel MR, Graamans K, Huizing EH. Influence of cocaine and lidocaine on human nasal ciliary beat frequency and harmony in vitro. *Archives of Otolaryngology, Head and Neck Surgery* 1994; **120**: 197–201.
20. Groth ML, Langenback EG, Foster WM. Influence of inhaled atropine on lung mucociliary function. *American Review of Respiratory Disease* 1991; **144**: 1042–1047.
21. Ingels KJAO, Meeuwsen F, Graamans K, Huizing EH. Influence of sympathetic and parasympathetic substances in clinical concentrations on human nasal ciliary beat. *Rhinology* 1992; **30**: 149–160.
22. Rogers DF, Barnes PJ. Opioid inhibition of neurally mediated mucus secretion in human bronchi. *Lancet* 1989; **1**: 930–931.
23. Rhodin JG. Ultrastructure and function of the human tracheal mucosa. *American Review of Respiratory Disease* 1966; **93**: 1–15.

British Journal of Anaesthesia 1996; **76**: 278–283

Electromyographic and mechanomyographic characteristics of neuromuscular block by magnesium sulphate in the pig†

C. LEE, X. ZHANG AND W.-F. KWAN

Summary

In spite of its well known propensity to cause accidental paralysis by a specific mechanism of action, Mg^{2+}-induced neuromuscular block has not been examined systematically for its characteristics of muscle response to nerve stimulation. We examined in seven anaesthetized domestic pigs the mechanomyographic (MMG) and neurally evoked compound electromyographic (ncEMG, EMG) responses of the tibialis anterior muscle to stimulation of its motor nerve, at baseline and during three levels of neuromuscular block induced by infusion of $MgSO_4$ (at approximately 25%, 50% and 75% depression of the 0.1-Hz EMG). We observed that: at 0.1 Hz, the MMG tended to be more depressed than the EMG; the train-of-four (2 Hz) was essentially non-fading; the tetanic force (50 Hz) showed tetanic ascent instead of tetanic fade and reached its baseline control value at 5 s in spite of depression of the twitch; the EMG counterpart of the tetanus showed escalation of the train of ncEMG, so that the fourth ncEMG was much greater than the first; and the post-tetanic twitch was also relatively spared from Mg^{2+}-induced neuromuscular block. Sparing of the tetanus and post-tetanic twitch resulted in large gains in the tetanus:twitch ratio and the post-:pre-tetanic twitch ratio, which increased at the 75% level of depression from 2.8 (SD 0.7) to 11.5 (4.0), and from 1.5 (0.3) to 4.6 (1.4) ($P < 0.01$), respectively. These characteristics of neuromuscular block by Mg^{2+} reflect its prejunctional mechanism of action by depression of transmitter release. (*Br. J. Anaesth.* 1996; **76**: 278–283)

Key words

Ions, magnesium. Neuromuscular block, measurement of response. Measurement technique, mechanomyography. Measurement technique, electromyography. Pig.

The non-depolarizing neuromuscular block produced by blockers of the curare-type ("curariform") is recognized by train-of-four (TOF) fade, tetanic fade and post-tetanic enhancement of twitch response ('post-tetanic potentiation'). In comparison, depolarizing neuromuscular block does not manifest fade or post-tetanic potentiation, but the changing nature of its block from phase I to phase II is recognized by these signs [1, 2]. Between the non-depolarizing and depolarizing blocks, mechanomyographic (MMG) and electromyographic (EMG) responses to motor nerve stimulation differ in relative sensitivity [1]. Fade observed during curariform neuromuscular block *in vivo* is generally attributed to diminution of successive end-plate potentials (EPP) observed *in vitro*, which in turn is attributed to depression of acetylcholine mobilization prejunctionally [3]. TOF fade [4] has yielded the "TOF count" [5], a method which is now used as a routine to estimate curariform neuromuscular block clinically. The diminishing TOF ratio during continuous administration of suxamethonium is also useful in defining phase II *vs* phase I neuromuscular block [2, 6]. At the end of surgery, these monitoring techniques also guide dosing and reversal of neuromuscular block in anaesthetic practice.

In contrast with the extensive literature on curariform and depolarizing neuromuscular blocks, there is a remarkable paucity of literature on the features of magnesium-induced neuromuscular block *in vivo*. Many reports have documented accidental paralysis as a side effect of magnesium sulphate ($MgSO_4$) therapy [7]. Magnesium (Mg^{2+}) blocks prejunctionally, with a different mechanism of action from the curariform and depolarizing blockers.

As indications for $MgSO_4$ therapy have increased rapidly [8, 9], we feel that Mg^{2+} deserves an independent study of its neuromuscular blocking characteristics. We have recently quantified the dose–response relationship of Mg^{2+}-induced neuromuscular block in an animal model while studying the effect of Mg^{2+} on the refractoriness of neuromuscular transmission [10]. The present study describes in qualitative and quantitative terms the MMG and EMG responses to motor nerve stimulation during three levels of Mg^{2+}-induced neuromuscular block.

Materials and methods

With institutional approval, seven male Duroc brown pigs, 9–12 kg, were anaesthetized with pentobarbitone 50 mg kg^{-1} i.p., supplemented with

---

CHINGMUH LEE, MD, XIAOYAN ZHANG, MD, WING-FAI KWAN, MD, Department of Anesthesiology, Harbor-UCLA Medical Center, Torrance, CA 90509-2910, USA. Accepted for publication: September 5, 1995.

† Presented in part at the Annual Meeting of the American Society of Anesthesiologists, October 24, 1995, Atlanta, Georgia, USA.

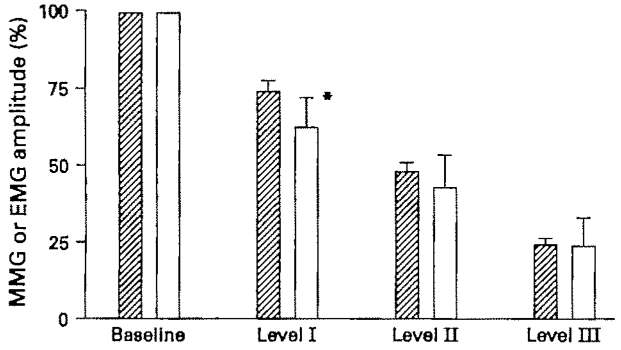


Figure 1 Differential depression by Mg^{2+} of the neurally evoked 0.1-Hz MMG (□) and EMG (▨) responses from their respective baselines at approximately 25 % (level I), 50 % (level II) and 75 % (level III) depression of the ncEMG.

2–5 mg kg^{-1} i.v. as required during the study. A cuffed tracheal tube of 6-mm internal diameter was inserted and ventilation of the lungs was controlled with a Harvard respirator pump at a rate of 15 times per minute. Tidal volume of air was adjusted to maintain an end-expiratory carbon dioxide concentration of 4–4.5 %. A cannula was inserted into a carotid artery for continuous monitoring of arterial pressure. A peripheral venous cannula was inserted for hydration and infusion of $MgSO_4$. Each pig received approximately 120–180 ml of 5 % glucose in normal saline during the entire experiment. The oesophageal temperature was maintained at 36–38 °C by a heating lamp. A pair of fine Grass EEG platinum solid needle electrodes (type E2) were inserted s.c., slightly posterior and distal to the proximal head of the fibula. Several attempts were made to position these electrodes close together (1–2 mm at the tips) and as close to the common peroneal nerve as possible, so that the electrical stimulus required for supramaximal stimulation and the stimulus artefact were as small as possible.

Three other identical electrodes were used for detection of the neurally evoked compound electromyogram (ncEMG), as described previously [11]. Guided by palpation of the twitch, the sensing electrode was inserted s.c. along the frontal aspect of the tibialis anterior muscle, crosswise to the muscle at its belly. A reference electrode was inserted s.c. near the insertion of this muscle, away from all muscles. A reference electrode was inserted s.c. between the stimulating and sensing pairs of electrodes. The EMG sensing electrode was repositioned several times to assure an optimal waveform, without double peaking or excessive stimulus artefact. Each preparation must produce a stable unipolar waveform typical of the ncEMG, as described previously [11], before the experiment can begin. The electric stimuli were generated by a Grass S88 stimulator and passed through a Grass SIU5 stimulus isolation unit. The supramaximal stimulus was determined, and 20–50 % of the voltage added. The stimulus was rectangular and of 0.1 ms duration. The ncEMG response was digitized, processed and reconverted to analogue waveforms for immediate online recording, as described previously [12]. Side by side with the ncEMG, the MMG response of the same tibialis anterior muscle was recorded simultaneously. The tendon was detached from its insertion with a chip of bone, freed from constraints and connected to a Grass force displacement transducer (FT10C). The motor nerve was stimulated at 0.1 Hz. Periodically (see below) the 0.1-Hz stimulation was interrupted for TOF (2 Hz) and tetanic (50 Hz, 5 s) stimulations. The first post-tetanic 0.1-Hz stimulation was delivered 5 s after the tetanus. Of the 250 ncEMG responses corresponding to a 50-Hz, 5-s tetanus, the first four could be processed and recorded in time before the first post-tetanic twitch was evoked. These four were recorded online for analysis.

After the preparation had stabilized for 30–45 min,

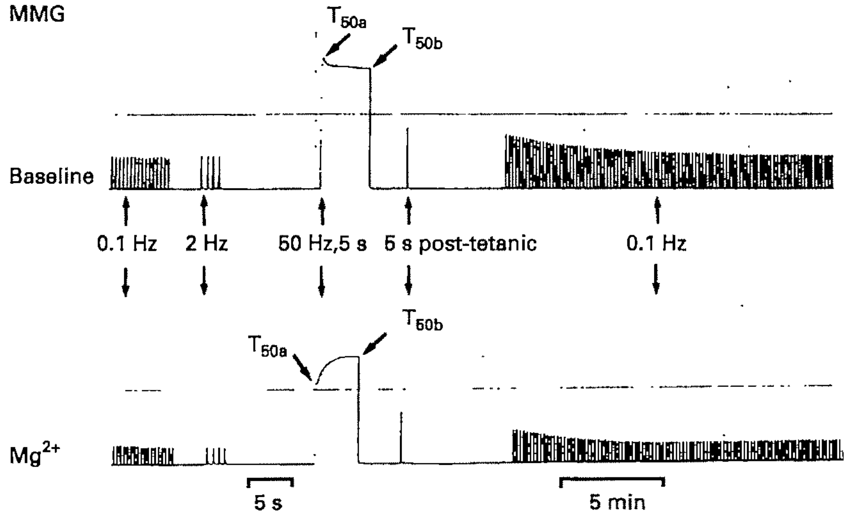


Figure 2 Neurally evoked MMG twitch (0.1 Hz), TOF (2 Hz), tetanus (50 Hz, 5 s) and post-tetanic twitches at baseline (upper panel) and during Mg^{2+}-induced neuromuscular block (lower panel). Note the increasing tetanus ("tetanic ascent") during neuromuscular block. In this experiment, the 0.1-Hz twitch was depressed by 45 %. TOF responses neither clearly faded nor escalated at baseline or during block. The tetanus was sustained at baseline. It was depressed by 32 % during block, but increased steadily so that at 5 s it was depressed by only 11 % from baseline. The post-tetanic twitch was potentiated at baseline. The potentiation was augmented during block, so that the post-tetanic twitch was depressed by only 16 % from baseline.

baseline values of a series of EMG and MMG responses were obtained. The series consisted of 0.1 Hz ("twitch"), TOF, tetanic and post-tetanic responses. $MgSO_4$ was then infused to establish three levels of neuromuscular block in succession, at approximately 25%, 50% and 75% depression of the 0.1-Hz EMG. Each level, when established, was maintained 5–10 min at the end of which a series of twitch, TOF, tetanic and post-tetanic responses were again obtained. Because various EMG and MMG variables of response were expected to differ, the three levels of neuromuscular block were established according to the amplitude of the 0.1-Hz EMG, irrespective of other variables. Levels I, II and III therefore refer to approximately 25%, 50% and 75% depression of the amplitude of the 0.1-Hz ncEMG, respectively. Data are expressed as mean (SD), and paired data sets were compared with repeat measures ANOVA or Student's paired t test (two-tailed). $P < 0.05$ was considered statistically significant.

Results

The three levels of neuromuscular block actually established were 25 (3)%, 51 (3)% and 74 (2)% depression of the ncEMG, respectively (fig. 1). The MMG twitch response tended to be more depressed than the EMG counterpart. Figure 2 illustrates the MMG twitch, TOF, tetanic and post-tetanic twitch responses at baseline and during Mg^{2+}-induced neuromuscular block. Figure 3 illustrates the EMG counterparts. The TOF ratio at control was 1 with every experiment. The TOF responses remained non-fading in character during all levels of Mg^{2+}-induced neuromuscular block, although the EMG and MMG TOF ratios were both slightly but consistently diminished from 1 ($P < 0.05$) to approximately 0.9.

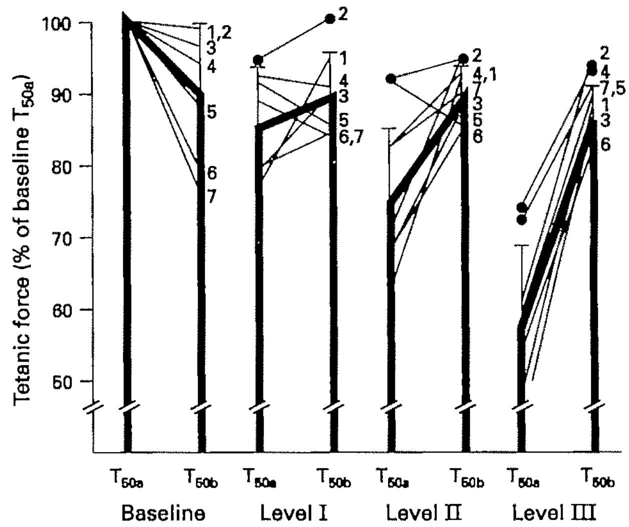


Figure 4 Tetanic ascent observed during Mg^{2+}-induced neuromuscular block. The thick line = the 5-s tetanus; the vertical error bars = SD. T_{50a} and T_{50b} = tetanic force at the beginning and end of the 5-s, 50-Hz tetanus, respectively. The thin numbered horizontal or slanting lines = individual pigs. Level tetanus at baseline (pigs 1, 2) ascended with any neuromuscular block, while fading tetanus at baseline (pigs 5, 6, 7) reversed at deeper levels of block to show an ascent.

Mg^{2+}-induced neuromuscular block did not cause tetanic fade. Instead, it caused a tetanic increase so that the tetanic contractile force was greater at 5 s (fig. 2, T_{50b}) than at the beginning of tetanus (fig. 2, T_{50a}). Figure 4 shows the varied behaviour of the tetanus among pigs. Some pigs showed mild tetanic fade at baseline, which reversed at various levels of neuromuscular block to become a tetanic increase. At deeper levels of block, all pigs showed marked tetanic increase. Corresponding with the tetanic ascent, the fourth ncEMG of the tetanus was much greater in amplitude than the first during neuromuscular block (fig. 3, 50 Hz; fig. 5).

The tetanus was spared from Mg^{2+}-induced neuromuscular block (fig. 6). Comparing the contractile forces at 5 s (T_{50b}), the tetanus elicited during $MgSO_4$ infusion did not show a statistically significant difference from the tetanus elicited at baseline ($P > 0.5$ for all three levels). The post-tetanic twitch was also spared markedly, although not completely.

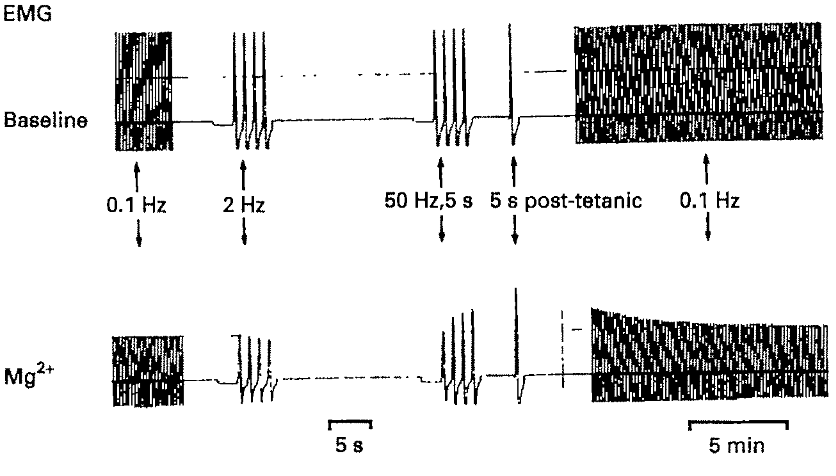


Figure 3 Neurally evoked compound EMG responses at baseline (upper panel) and during Mg^{2+}-induced neuromuscular block (lower panel). The TOF responses (2 Hz) did not fade at baseline but faded slightly during block. The next four ncEMG responses, marked "50 Hz, 5 s", represent the first 80 ms of the 5-s tetanus. They showed marked escalation during neuromuscular block. This escalation is the EMG counterpart of the increasing tetanic force. As is in the case of the MMG, the 5-s post-tetanic twitch was less depressed than the pre-tetanic twitch. The 50 Hz and 2 Hz EMG were displaced with the same spacing for clarity [11, 12].

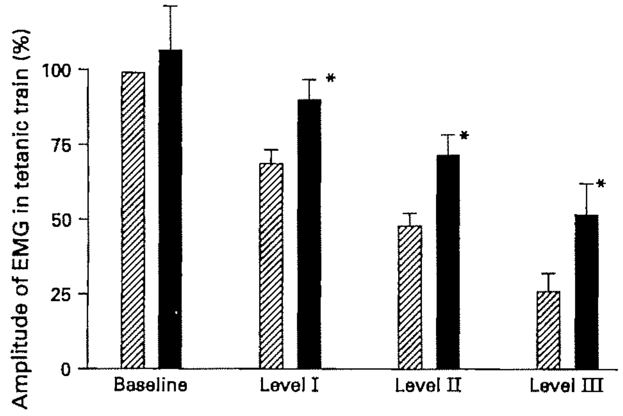


Figure 5 The first (▨) and fourth (■) of the train of ncEMG of a tetanus (50 Hz) evoked at baseline and at three levels of Mg^{2+}-induced neuromuscular block. At each level, the first ncEMG corresponds to the singly evoked ncEMG (0.1 Hz) and shows the degree of neuromuscular block. The fourth ncEMG was relatively spared from the block. The fourth : first ratio increased from 1.1 (0.2) to 1.3 (0.1), 1.5 (0.1) and 2.0 (0.2) at the three levels of block, respectively ($P < 0.05$). The discrete EMG escalated as the fused tetanic contraction ascended.

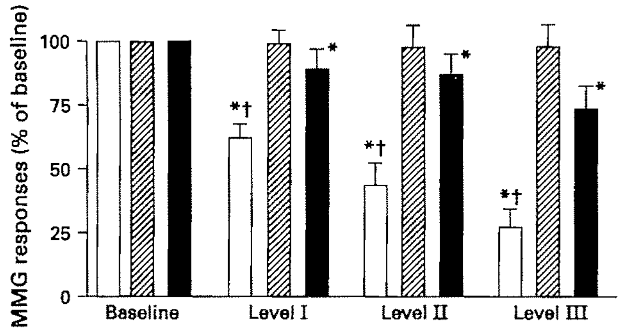


Figure 6 Sparing of tetanus (▨) and post-tetanic twitch (■) from Mg^{2+}-induced neuromuscular block. Tetanic force (50 Hz, 5 s) was measured at 5 s, as the T_{50b}. The post-tetanic twitch was evoked 5 s after the end of the tetanus. Note that the tetanic force measured at 5 s did not diminish from baseline ($P > 0.5$, all three levels) in spite of depression of the twitch (□). The post-tetanic twitch was slightly depressed from baseline ($P < 0.05$), but less so than the twitch at any level ($P < 0.01$).

As a result of tetanic and post-tetanic sparing, the tetanus : twitch ratio and post- : pre-tetanic twitch ratio were increased markedly (table 1).

Discussion

There is a clear distinction between prejunctional and postjunctional sites of action and between mobilization and release mechanisms of the prejunctional actions of neuromuscular blocking agents. For decades, Mg^{2+} has been recognized as the prototype of the latter mechanism of prejunctional neuromuscular block *in vitro* [13]. It causes accidental paralysis by itself or in interaction with other neuromuscular blockers *in vivo*. In addition to obstetric use, Mg^{2+} is being used increasingly by paediatricians [14], endocrinologists [15], cardiologists [16–19], cardiac surgeons [20] and emergency [21, 22] and other specialists [8, 23]. Examples of new indications for $MgSO_4$ which are of interest to anaesthetists are phaeochromocytoma [24–26], refractory cardiac arrhythmia [16] and resuscitation [21, 22]. A method of diagnosis of Mg^{2+}-induced neuromuscular block by nerve stimulation therefore deserves exploration.

According to our results, Mg^{2+}-induced neuromuscular block may be characterized as follows: the MMG response tends to be more depressed than the EMG response; TOF responses do not fade; tetanus does not fade, instead its contractile force increases; the train of successive EMG responses during tetanic stimulation escalate; the peak tetanic force does not diminish although the tetanus starts at a lower point; and the physiological potentiation of the post-tetanic twitch is augmented so that the post-tetanic twitch is relatively spared. As a result of tetanic and post-tetanic sparing, the tetanus : twitch ratio and the post- : pre-tetanic twitch ratio increase markedly This set of characteristics clearly distinguish Mg^{2+}-induced neuromuscular block from curariform, phase I (depolarizing), phase II (post-depolarizing, desensitization) and post-junctional irreversible non-depolarizing (α-bungarotoxin) types of neuromuscular block [27] (table 2).

TOF fade is explained by diminution in successive EPP, which result from depressed mobilization of the transmitter, which in turn is caused by occupation of the prejunctional "mobilization receptors", according to Bowman [3]. This theory requires that neuromuscular block achieved by occupation of postjunctional receptors alone, such as by .α-bungarotoxin, does not manifest tetanic or TOF fade. This, indeed, is the case [27]. In the case of Mg^{2+}, our observations are explicable by the generally accepted main mechanism of neuromuscular action of Mg^{2+}, which is depression of prejunctional release of acetylcholine. As successive motor impulses lead to accumulation of Ca^{2+} in the motor nerve terminal, successive EPP become less depressed by Mg^{2+}. This escalation of the train of EPP results in "tetanic escalation" of the ncEMG responses. It also causes the increasing tetanic force ("tetanic ascent") which spares the tetanus from depression. The enhanced post-tetanic potentiation can similarly be explained by accumulation of Ca^{2+} during tetanic stimulation. The MMG twitch tends to be more depressed than its corresponding EMG because Mg^{2+} is also thought to directly depress the contractility of the muscle [13]. The reason for the slight TOF fade is unclear. Ramanathan and colleagues [28] reported TOF escalation in pre-eclamptic patients. Toxaemia of pregnancy may account for the difference. In any case, the TOF ratio did not change by more than 10% from baseline.

From the above, it becomes obvious that the word "non-depolarizing" is generic and fails to distinguish prejunctional (mobilization, release) and postjunctional (competitive, non-competitive) non-depolarizing neuromuscular blocks from curariform (mobilization and competitive) block (table 2). Because of this, we prefer to call neuromuscular block of the curare type "curariform" block, to facilitate its distinction from other types of non-depolarizing neuromuscular block, including the "release block" by Mg^{2+}.

Table 1 Tetanus and post-tetanic twitch, as multiples of the pre-tetanic twitch, during 25% (level I), 50% (level II) and 75% (level III) Mg^{2+}-induced depression of the 0.1-Hz ncEMG. *$P < 0.05$: level I, II or III *vs* baseline values, both rows

	Baseline	Level I	Level II	Level III
Tetanus: twitch ratio*	2.7 (0.7)	4.6 (1.7)	6.7 (2.7)	11.5 (4.3)
Post-: pre-tetanic twitch ratio	1.5 (0.3)	2.2 (0.6)	3.0 (0.9)	4.6 (1.4)

Table 2 Patterns of mechanomyographic neuromuscular responses to nerve stimulation distinguishing various mechanisms of neuromuscular block *in vivo*

	$MgSO_4$	Phase I	Phase II	Curariform	α-Bungarotoxin
MMG *vs* EMG	More sensitive	Less sensitive	?	More sensitive	?
TOF fade	Negligible	Negligible	Emerges	Marked	Negligible
Tetanus	Increases	Level	Fade emerges	Fades	Level
Tetanus sparing	Marked	?	?	Clear	?
Post-tetanic twitch potentiation	Marked	Minimal	Emerges	Marked	Clear

The clinical implications of our observations can only be speculative at present, and only a few obvious possibilities are examined below. First, neuromuscular block by the same mechanism of action should exhibit similar or the same patterns of response to nerve stimulation. Aminoglycoside antibiotics block neuromuscular transmission mainly by competition with Ca^{2+}, as is the case with Mg^{2+} [29, 30]. In agreement with this, we have previously observed that streptomycin and neomycin also block neuromuscular transmission with tetanus and post-tetanic sparing [31]. We surmise that the extremely high mortality associated with antibiotic-induced neuromuscular block in the 1970s might be partially attributable to failure to differentially diagnose aminoglycoside-induce neuromuscular block from curariform or depolarizing neuromuscular block [32].

Second, humans usually exhibit similar qualitative patterns of neuromuscular block as do most laboratory animals. Quantitatively, domestic pigs are useful for predicting human responses to neuromuscular blocking agents [33, 34]. As escalation of the train of ncEMG responses in the beginning of tetanus is a consistent and clear-cut finding, a very brief burst of nerve stimuli delivered rapidly might be the best candidate for clinical development as a diagnostic tool of Mg^{2+}-induced neuromuscular block. Such a brief single burst of stimulation should cause no greater pain than the double-burst stimulation. Similar to the TOF [4] or count [5], the escalation ratio and the tetanus: twitch ratio require no historical control for quantitative assessment of neuromuscular block.

Third, tetanic sparing should imply that in spite of depression of the twitch, physiological muscle functions, all of which are tetanic in nature, may be well preserved. The fact that the tetanic force takes a few seconds to reach maximum may imply that sustained motions such as headlift or breathing may be less depressed than brisk motions such as knee jerk or cough. Indeed, toxaemic patients are often given $MgSO_4$ until the knee jerk disappears, without obvious loss of ability to lift the head and to breathe. On the one hand, therefore, tetanic sparing represents a margin of safety of physiological functions. On the other hand, however, this pattern of paresis may lead to failure to observe Mg^{2+}-induced neuromuscular block clinically, which is a danger. Finally, in a patient who has previously received both $MgSO_4$ and a curariform blocker, detection of TOF and tetanic fades should reveal the continuous presence of the curariform block while demonstration of a tetanic ascent should imply dominance of Mg^{2+}-induced neuromuscular block. A level tetanus may imply absence of any neuromuscular block or a balance of tetanic fade and tetanic ascent.

References

1. Katz RL. Electromyographic and mechanical effects of suxamethonium and tubocurarine on twitch, tetanic and post-tetanic responses. *British Journal of Anaesthesia* 1973; **45**: 849–859.
2. Lee C. Dose relationships of phase II, tachyphylaxis and train-of-four fade in suxamethonium-induced dual neuromuscular block in man. *British Journal of Anaesthesia* 1975; **47**: 841–845.
3. Bowman WC. Prejunctional and postjunctional cholinoceptors at the neuromuscular junction. *Anesthesia and Analgesia* 1980; **59**: 935–943.
4. Ali HH, Utting JE, Gray TC. Quantitative assessment of residual antidepolarizing block (Part I). *British Journal of Anaesthesia* 1971; **43**: 473–477.
5. Lee C. Train-of-4 quantitation of competitive neuromuscular block. *Anesthesia and Analgesia* 1975; **54**: 649–653.
6. Ramsey FM, Lebowitz PW, Savarese JJ, Ali HH. Clinical characteristics of long-term succinylcholine neuromuscular blockade during balanced anesthesia. *Anesthesia and Analgesia* 1980; **59**: 110–116.
7. Gambling DR, Birmingham CL, Jenkins LC. Magnesium and the anaesthetist. *Canadian Journal of Anaesthesia* 1988; **35**: 644–654.
8. James MFM. Clinical use of magnesium infusions in anesthesia. *Anesthesia and Analgesia* 1992; **74**: 129–136.
9. Zaloga G, Eisenach JC. Magnesium, anesthesia, and hemodynamic control. *Anesthesiology* 1991; **74**: 1–2.
10. Lee C, Zhang X, Kwan WF. Neuromuscular refractoriness, prejunctional block and $MgSO_4$ in the pig. *Anesthesia and Analgesia* 1995; **80**: S270.
11. Lee C, de Silva AJC, Katz RL. Multipeaking of the compound electromyographic response to single nerve stimulus: Its occurrence and prevention in an experimental model. *British Journal of Anaesthesia* 1978; **50**: 459–462.
12. Lee C, Katz RL, Lee ASJ, Glaser B. A new instrument for

continuous recording of the evoked compound electromyogram in the clinical setting. *Anesthesia and Analgesia* 1977; **56**: 260–270.

13. del Castillo J, Engbaek L. The nature of the neuromuscular block produced by magnesium. *Journal of Physiology (London)* 1954; **124**: 370–384.
14. Abu-Osba YK, Galal O, Manasra K, Rejjal A. Treatment of severe persistent pulmonary hypertension of the newborn with magnesium sulphate. *Archives of Disease in Childhood* 1992; **67**: 31–35.
15. Nadler JL, Malayan S, Luong H, Shaw S, Natarajan RD, Rude RK. Intracellular free magnesium deficiency plays a key role in increased platelet reactivity in type II diabetes mellitus. *Diabetes Care* 1992; **15**: 835–841.
16. Tzivoni D, Banai S, Schuger C, Benhorin J, Keren A, Gottlieb S, Stern S. Treatment of torsade de pointes with magnesium sulfate. *Circulation* 1988; **77**: 392–397.
17. Woods KL, Fletcher S, Roffe C, Haider Y. Intravenous magnesium sulphate in suspected acute myocardial infarction: results of the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet* 1992; **339**: 1553–1558.
18. Gottlieb SS, Fisher ML, Pressel MD, Patten RD, Weinberg M, Greenberg N. Effects of intravenous magnesium sulfate on arrhythmias in patients with congestive heart failure. *American Heart Journal* 1993; **125**: 1645–1650.
19. Roffe C, Fletcher S, Woods KL. Investigation of the effects of intravenous magnesium sulphate on cardiac rhythm in acute myocardial infarction. *British Heart Journal* 1994; **71**: 141–145.
20. O-Yurvati AH, Sanders SP, Dullye LJ, Carney MP, Archer RL, Koro PP. Antiarrhythmic response to intravenously administered magnesium after cardiac surgery. *Southern Medical Journal* 1992; **85**: 714–717.
21. Craddock L, Miller B, Clifton G, Krumbach B, Pluss W. Resuscitation from prolonged cardiac arrest with high-dose intravenous magnesium sulfate. *Journal of Emergency Medicine* 1991; **9**: 469–476.
22. Kuitert LM, Kletchko SL. Intravenous magnesium sulfate in acute, life-threatening asthma. *Annals of Emergency Medicine* 1991; **20**: 1243–1245.
23. Olerich MA, Rude RK. Should we supplement magnesium in critically ill patients? *New Horizons* 1994; **2**: 186–192.
24. James MFM. Use of magnesium sulfate in the anaesthetic management of phaeochromocytoma: a review of 17 anaesthetics. *British Journal of Anaesthesia* 1989; **62**: 616–623.
25. James MFM, Huddle KRL, Owen AD, van der Veen BW. Use of magnesium sulphate in the anaesthetic management of phaeochromocytoma in pregnancy. *Canadian Journal of Anaesthesia* 1988; **35**: 178–182.
26. Drolet P, Girard M. L'utilisation du sulfate de magnésium pendant la chirurgie du phéochromocytome: à propos de deux cas. *Canadian Journal of Anaesthesia* 1993; **40**: 521–525.
27. Lee C, Chen D, Katz RL. Characteristics of nondepolarizing neuromuscular block: (I) post-junctional block by alpha-bungarotoxin. *Canadian Anaesthetists Society Journal* 1977; **24**: 212–219.
28. Ramanathan J, Sibai BM, Pillai R, Angel JJ. Neuromuscular transmission studies in preeclamptic women receiving magnesium sulfate. *American Journal of Obstetrics and Gynecology* 1988; **158**: 40–46.
29. Singh YN, Marshall IG, Harvey AL. Pre- and postjunctional blocking effects of aminoglycoside, polymyxin, tetracycline and lincosamide antibiotics. *British Journal of Anaesthesia* 1982; **54**: 1295–1306.
30. Sokoll MD, Gergis SD. Antibiotics and neuromuscular function. *Anesthesiology* 1981; **55**: 148–159.
31. Lee C, Chen D, Barnes A, Katz RL. Neuromuscular block by neomycin in the cat. *Canadian Anaesthetists Society Journal* 1976; **23**: 527–533.
32. Pittinger CB, Eryasa Y, Adamson R. Antibiotic-induced paralysis. *Anesthesia and Analgesia* 1970; **49**: 487–501.
33. Muir AW, Marshall RJ. Comparative neuromuscular blocking effects of vecuronium, pancuronium, Org 6368 and suxamethonium in the anaesthetized domestic pig. *British Journal of Anaesthesia* 1987; **59**: 622–629.
34. Muir AW, Marshall RJ. Is the anaesthetized domestic pig a better model than the cat for predicting neuromuscular (N-M) blocking activity in man? *European Journal of Pharmacology* 1990; **183**: 2011.

British Journal of Anaesthesia 1996; **76**: 284–291

A model to describe the rate of oxyhaemoglobin desaturation during apnoea

A. D. FARMERY AND P. G. ROE

Summary

We have developed a model to describe the rate of oxyhaemoglobin desaturation during apnoea. This model takes into account the non-steady-state kinetics which pertain to this situation. We first derived a mathematical expression for instantaneous oxygen flux rate from the alveolar compartment. We then derived an expression to describe the effect of shunt on this flux. The effect of circulation time on real-time arterial mixed venous oxygen content difference and oxygen flux in the lung was determined graphically. We finally described a manoeuvre to accommodate the effect of the Bohr shift which is related to the increase in $F\text{A}_{CO_2}$ during apnoea. We present plots of arterial oxyhaemoglobin saturation (Sa_{O_2}) *vs* duration of apnoea to illustrate the individual effects of the initial fractional concentration of oxygen in the alveolus ($F\text{A}_{O_2(initial)}$), alveolar volume ($V\text{A}$), shunt fraction ($\dot{Q}\text{S}/\dot{Q}\text{T}$), oxygen consumption rate ($\dot{V}O_2$), total blood volume ($Q\text{T}$) and haemoglobin concentration (Hb). The model is illustrated by examples of paediatric, morbidly obese and postoperative scenarios. The postoperative scenario is particularly notable for the effect of a combination of small changes in individual variables leading to a large overall effect on the rate of oxyhaemoglobin desaturation. (*Br. J. Anaesth.* 1996; **76**: 284–291)

Key words

Oxygen, saturation. Ventilation, apnoea. Model, pharmaco-physiological.

Apnoea may occur both during anaesthesia and in the postoperative period for many reasons. The principal consequence of this depends on the rate at which the oxyhaemoglobin saturation of arterial blood (Sa_{O_2}) is reduced to unacceptable levels and there are clearly many relevant factors. In order to study the factors affecting the rate of oxyhaemoglobin desaturation, it was necessary to construct a model.

It might appear *a priori* that the rate at which oxyhaemoglobin desaturation occurs is simply determined by the ratio of the oxygen consumption rate ($\dot{V}O_2$) to the alveolar reserve volume of oxygen ($V\text{A}$). However, such a model is too simplistic and has been criticized [1] because it is based on steady-state kinetics, and apnoea is a non-steady state event. In the non-steady state, the rate of oxygen flux from the alveoli to the pulmonary capillaries is not constant and the shunt equation is not easily soluble. There is also a time lag between changes in arterial oxygen content and corresponding changes in mixed venous oxygen content because of the circulation time which affects the rate of alveolar oxygen exchange at any time. In addition to the alveolar oxygen volume at the beginning of apnoea, circulating blood also serves as an oxygen store which is in a dynamic equilibrium with the diminishing alveolar store. The reduction in Sa_{O_2} is moderated by the reservoir of oxygen in the alveoli.

The obligatory increase in arterial carbon dioxide partial pressure (Pa_{CO_2}) and the consequent decrease in pH during apnoea has an effect on the oxygen–haemoglobin dissociation curve (ODC) such that the affinity of haemoglobin for oxygen varies as a function of time throughout apnoea (dynamic Bohr shift). This too might be expected to affect the rate of oxyhaemoglobin desaturation.

We therefore present a comprehensive model which incorporates the above considerations to describe the rate of arterial oxyhaemoglobin desaturation in the non-steady state in various pathophysiological states.

Theoretical considerations

We made several assumptions in constructing the model. We assumed that lung volume remains constant during apnoea. In fact, lung volume diminishes slightly during apnoea because oxygen is removed to a slightly greater extent than carbon dioxide accumulates, assuming that the value of the respiratory quotient is < 1. A three-compartment model of shunt, ideal alveoli and deadspace was used to model the lung. Gas mixing was assumed to be complete within the ideal alveoli. Circulation of blood was modelled as a single unit of given mean transmit time (Δt_c) in which no mixing of blood occurs.

In the equations which follow, unless otherwise stated, all gas and blood volumes are expressed in litres, time is expressed in minutes and gas partial pressures are expressed as fractions of one standard atmosphere (101.325 kPa, BTPS) and are dimensionless. Haemoglobin concentration (Hb) is ex-

---

A. D. FARMERY, BSC, MB, BS, FRCA, P. G. ROE, BSC, MB, BS, FRCA, Department of Anaesthesia, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ. Accepted for publication: September 5, 1995.

pressed in g litre^{-1}. The dimensions of terms with compound units such as flow and gas contents are expressed in terms of the primary dimensions listed above. $K\mathrm{h}$ = Hüfner constant (1.34×10^{-3} litre g^{-1}). All fractional concentrations (F) refer to oxygen and all saturations (S) refer to arterial oxyhaemoglobin, unless otherwise stated.

AN EXPRESSION FOR THE INSTANTANEOUS OXYGEN FLUX RATE FROM THE ALVEOLAR COMPARTMENT

Let the quantity of oxygen in the apnoeic lung be ($V\mathrm{A} \times F\mathrm{A}$) where $V\mathrm{A}$ = alveolar volume and $F\mathrm{A}$ = fractional concentration of oxygen in alveolar gas ($F\mathrm{A}_{\mathrm{O}_2}$).

The rate of change of oxygen mass ($\dot{v}\mathrm{O}_2$)

$$= \mathrm{d}(V\mathrm{A} \times F\mathrm{A})/\mathrm{d}t$$

$$= V\mathrm{A} \times \mathrm{d}F\mathrm{A}/\mathrm{d}t + F\mathrm{A} \times \mathrm{d}V\mathrm{A}/\mathrm{d}t$$

It is important to appreciate that the term $\dot{v}\mathrm{O}_2$ = the instantaneous rate of oxygen uptake by the blood. It is a *variable* and a function of time. Only in the steady state is the term constant and equal to the term $\dot{V}\mathrm{O}_2$, the oxygen consumption rate in the tissues. As we have assumed that $V\mathrm{A}$ remains constant, $\mathrm{d}V\mathrm{A}/\mathrm{d}t$ equals zero and hence:

$$\dot{v}\mathrm{O}_2 = -V\mathrm{A} \times \mathrm{d}F\mathrm{A}/\mathrm{d}t \tag{1}$$

Notice the sign change resulting from the convention that oxygen uptake by the blood is nominally positive, and $\mathrm{d}F\mathrm{A}/\mathrm{d}t$ is negative.

AN EXPRESSION TO DESCRIBE THE EFFECTS OF SHUNT

The relatively small quantity of oxygen physically dissolved in blood has been ignored in order to simplify the mathematical analysis. In all cases, the error in predicted $S\mathrm{a}_{\mathrm{O}_2}$ incurred by this omission is less than 0.05%, although this is greater when the inspired fractional concentration of oxygen ($F\mathrm{I}_{\mathrm{O}_2}$) is 1 and under hyperbaric conditions.

The shunt fraction ($\dot{Q}\mathrm{s}/\dot{Q}\mathrm{T}$) = f_s

Then,

$$S\mathrm{a} = S\mathrm{c}' \times (1 - f_s) + f_s \times S\bar{\mathrm{v}} \tag{2}$$

where $S\mathrm{c}'$ = end-capillary oxyhaemoglobin saturation and $S\bar{\mathrm{v}}$ = mixed venous oxyhaemoglobin saturation, $\dot{Q}\mathrm{s}$ = shunted blood flow and $\dot{Q}\mathrm{T}$ = total cardiac output.

From Fick's principle,

$$\dot{v}\mathrm{O}_2 = \dot{Q}\mathrm{T} \times (\mathrm{Hb}) \times K\mathrm{h} \times (S\mathrm{a} - S\bar{\mathrm{v}})$$

$$S\bar{\mathrm{v}} = S\mathrm{a} - \dot{v}\mathrm{O}_2/\dot{Q}\mathrm{T} \times (\mathrm{Hb}) \times K\mathrm{h} \tag{3}$$

Combining equations (2) and (3) to eliminate $S\bar{\mathrm{v}}$,

$$S\mathrm{a} = S\mathrm{c}' - \left(\frac{f_s}{1 - f_s}\right) \times \frac{\dot{v}\mathrm{O}_2}{\dot{Q}\mathrm{T} \times (\mathrm{Hb}) \times K\mathrm{h}}$$

Let $S\mathrm{c}'$ be expressed in terms of $F\mathrm{A}$ (see appendix) and substituting $\dot{v}\mathrm{O}_2$ from equation (1) gives:

$$S\mathrm{a} = b \times \left(\frac{F\mathrm{A}^n}{F\mathrm{A}^n + F_{50}{}^n}\right) - \left(\frac{f_s}{1 - f_s}\right) \times \frac{V\mathrm{A} \times \mathrm{d}F\mathrm{A}/\mathrm{d}t}{\dot{Q} \times (\mathrm{Hb}) \times K\mathrm{h}} \tag{4}$$

This differential equation describes $S\mathrm{a}$ as a function of $F\mathrm{A}$ and $\mathrm{d}F\mathrm{A}/\mathrm{d}t$, both of which are functions of time. It is not yet soluble for $S\mathrm{a}$ in terms of time alone, as we have no independent expression of the time course of $F\mathrm{A}$. This problem is addressed in the next section.

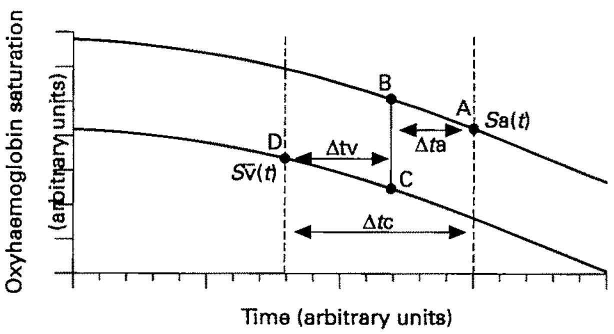


Figure 1 Putative time courses of "tissue arterial" (upper curve) and "tissue venous" (lower curve) oxyhaemoglobin saturation during apnoea (see text for further explanation).

CONSIDERATION OF THE TIME COURSES OF ARTERIAL AND VENOUS OXYHAEMOGLOBIN DESATURATION AT ANY PARTICULAR LOCUS

Oxyhaemoglobin saturation after the onset of apnoea may be thought of as having three dimensions; it varies not only with time, but also with its position within the circulation, and so has a spatial dimension. For example, at a time when arterial blood is just starting to desaturate in the lungs, blood "sampled" at a peripheral arterial site just proximal to the tissues is not yet desaturated because of the circulation time lag. Figure 1 shows a putative plot of the time courses of arterial and venous oxyhaemoglobin desaturation. These two-dimensional curves represent the oxyhaemoglobin saturation at tissue arterial (upper curve) and tissue venous (lower curve) loci, respectively, as time from the start of apnoea varies. This same diagram can be used to consider the spatial dimension of apnoeic desaturation. The X axis now no longer represents ***absolute*** apnoeic time, but the ***relative*** time from when saturation began to decrease at any particular locus. Thus points A, B, C and D which represent the *contemporaneous* saturation at four loci within the circulation are not aligned vertically because the transit times to these various loci are different. Point A represents the saturation of blood in the most proximal part of the arterial tree (pulmonary venous) at time t which is equal to $S\mathrm{a}(t)$. Point B represents the saturation of blood at the most distal part of the arterial tree (just proximal to the lumped tissues) at time t. Point C represents the saturation of blood at the most proximal part of the venous tree (just distal to the lumped tissues) at time t. Point D represents the saturation of blood at the most distal point of the venous tree (pulmonary arterial) at time t which is equal to $S\bar{\mathrm{v}}(t)$. The arterial and venous curves are separated by vertical displacement equal to $\dot{V}\mathrm{O}_2/\dot{Q}\mathrm{T} \times (\mathrm{Hb}) \times K\mathrm{h}$ which is derived from Fick's principle (i.e. equation (3) applied at the tissue level). The horizontal distance between A and B is the arterial transit time ($\Delta t\mathrm{a}$) and between C and D is the venous transit time ($\Delta t\mathrm{v}$). The total circulation time, $\Delta t\mathrm{c} = \Delta t\mathrm{a} + \Delta t\mathrm{v}$.

By inspection, mixed venous saturation at time t can be seen to be as follows:

$$S\bar{v}(t) = Sa(t-\Delta tc) - \frac{\dot{V}O_2}{\dot{Q}T \times (Hb) \times Kh} \qquad (5)$$

Any function with a fixed phase shift such as $Sa(t-\Delta tc)$ can be expressed in terms of the same function with zero shift, that is $Sa(t)$, using Taylor's expansion as follows:

$$Sa(t-\Delta tc) = Sa(t) - \Delta tc \times \frac{dSa(t)}{dt} - \frac{\Delta tc^2}{2!} \times \frac{d^2Sa(t)}{dt^2} + \ldots \qquad (6)$$

So the *contemporaneous*, real-time arterial mixed venous oxyhaemoglobin saturation difference in the lung can be expressed as follows by combining equations (5) and (6):

$$Sa(t) - Sv(t) = \Delta tc \times \frac{dSa(t)}{dt} + \frac{\Delta tc^2}{2!} \times \frac{d^2Sa(t)}{dt^2} + \frac{\dot{V}O_2}{\dot{Q}T \times (Hb) \times Kh}$$

Fick's principle dictates that this saturation difference, when multiplied by the product of cardiac output, haemoglobin concentration and Huffner constant equals the instantaneous oxygen flux ($\dot{v}O_2$) from the alveolus to the pulmonary capillary blood at time t.

Hence,

$$\dot{Q}T \times (Hb) \times Kh \times \left(\Delta tc \times \frac{dSa(t)}{dt} + \frac{\Delta tc^2}{2!} \times \frac{d^2Sa(t)}{dt^2} + \frac{\dot{V}O_2}{\dot{Q}T \times (Hb) \times Kh}\right) = \dot{v}O_2 \qquad (7)$$

Combining equations (1) and (7) we have:

$$\Delta tc \times \frac{dSa(t)}{dt} + \frac{\Delta tc^2}{2!} \times \frac{d^2Sa(t)}{dt^2} + \frac{\dot{V}O_2}{\dot{Q}T \times (Hb) \times Kh} = \frac{V\text{A} \times dF\text{A}(t)/dt}{\dot{Q}T \times (Hb) \times Kh}$$

By integration with respect to time, and application of the appropriate limits, this yields the following equation, given that when $t = 0$: $F\text{A} = F\text{A}, 0$, $Sa = Sa, 0$ and $dSa(t)/dt = 0$:

$$Sa(t) \times \Delta tc = Sa,0 \times \Delta tc - \frac{\dot{V}O_2 \times t}{\dot{Q}T \times (Hb) \times Kh} + \frac{V\text{A}(F\text{A},0 - F\text{A}(t))}{\dot{Q}T \times (Hb) \times Kh} - \frac{\Delta tc^2}{2!} \times \frac{dSa(t)}{dt}$$

Dividing throughout by Δtc, the term $\dot{Q}T$ (cardiac output) becomes QT (blood volume) and hence:

$$Sa(t) = Sa,0 - \frac{\dot{V}O_2 \times t}{QT \times (Hb) \times Kh} + \frac{V\text{A}(F\text{A},0 - F\text{A}(t))}{QT \times (Hb) \times Kh} - \frac{\Delta tc}{2!} \times \frac{dSa(t)}{dt} \qquad (8)$$

In common with equation (4), equation (8) is another differential equation, this time describing Sa in terms of $F\text{A}$, dSa/dt and t. Together these constitute a pair of simultaneous differential equations whose symbolic solution, although theoretically possible, is complicated. We therefore solved them iteratively by computer for real positive roots to yield values of Sa as t varies. An IBM compatible 486 PC was used using software written specifically for this purpose (this Microsoft Qbasic program is available from the authors on request).

A MANOEUVRE TO ACCOMMODATE THE EFFECT OF THE BOHR SHIFT DURING APNOEA

During the period of apnoea, as Pa_{O_2} decreases, so Pa_{CO_2} increases. This progressive hypercapnia produces a reduction in arterial pH. Both this reduction in arterial pH and the increase in Pa_{CO_2} independently affect the affinity of haemoglobin for oxygen.

Kelman's polynomial equation for the ODC [2] accommodates the Bohr shift by multiplying PO_2 (in mm Hg) by a correction factor to give a "virtual PO_2".

$$PO_2(\text{virtual}) = PO_2 \times 10^{[0.4\times(\text{pH}-7.4)+0.06\times(\log 40-\log PCO_2)]}$$

The F_{50} value for any given conditions of pH and FCO_2 (i.e. the "Bohr shift sensitive" value, dubbed F'_{50}) is therefore given by:

$$F'_{50} = \frac{F_{50,\text{standard}}}{10^{[0.4\times(\text{pH}-7.4)+0.06\times(\log 40-\log PCO_2)]}}$$

$$= \frac{F_{50,\text{standard}}}{\left(\frac{40}{[H^+]}\right)^{0.4} \times \left(\frac{0.0526}{FCO_2}\right)^{0.06}}$$

In acute respiratory acidosis, the resulting $[H^+]$ (nmol litre^{-1}) may be estimated from the following equation [3]:

$$[H^+] = 570(FCO_2) + 10$$

The F'_{50} value can therefore be calculated for any given FCO_2, and the greater the rate of increase of FCO_2 the more pronounced is the effect of the Bohr shift.

THE RATE OF INCREASE OF FCO_2 IN APNOEA

Carbon dioxide produced in the tissues is not deposited solely in the alveolar compartment but also in blood and other tissues. The great capacity for blood to combine with carbon dioxide buffers the rate of increase of Fa_{CO_2} such that abrupt changes in alveolar ventilation rate produce changes in Fa_{CO_2} which approach their steady-state values with half-lives of up to 14 min [4], where Fa_{CO_2} equals the fractional concentration of carbon dioxide with which arterial blood is in equilibrium.

The rate of increase of Fa_{CO_2} is given by:

$$\frac{dFa_{CO_2}}{dt} = \frac{\dot{V}CO_2}{V\text{A} + QT \times \frac{dCCO_2}{dF\text{A}_{CO_2}}}$$

where $\mathrm{d}C\mathrm{CO_2}/\mathrm{d}Fa_{\mathrm{CO_2}}$ = the slope of the carbon dioxide dissociation curve (carbon dioxide content in litres of carbon dioxide per litre of blood *vs* $Fa_{\mathrm{CO_2}}$). This slope is described by McHardy [5] and can be shown to be as follows:

$$\text{dissociation slope} = 178 \times m \times F\mathrm{CO_2}^{m-1}$$

$$\text{where} \qquad m = \frac{0.0448 \times (\mathrm{Hb}) + 6.3}{30}$$

In summary, therefore, given the haemoglobin concentration and initial $Fa_{\mathrm{CO_2}}$ value, the rate of increase of $Fa_{\mathrm{CO_2}}$ can be calculated. This allows calculation of $Fa_{\mathrm{CO_2}}$ and hence F'_{50} at any point in time. This latter value can be substituted into equation (4) to facilitate the computation of the time course of $Sa_{\mathrm{O_2}}$ incorporating the effects of the Bohr shift.

Results

The following conditions were applied in the model to produce a standard adult curve of $Sa_{\mathrm{O_2}}$ *vs* time (fig. 2, line B): (Hb) = 150 g litre^{-1}, cardiac output ($\dot{Q}\mathrm{T}$) = 5.0 litre min^{-1}, alveolar volume at resting expiratory level ($V\mathrm{A}$) = 2.5 litre, $\dot{V}\mathrm{O_2}$ = 0.25 litre min^{-1}, total blood volume ($Q\mathrm{T}$) = 5.0 litre, shunt fraction = 0, $F\mathrm{A}_{\mathrm{O_2}\,\mathrm{initial}} = 0.133$, $Fa_{\mathrm{CO_2}\,\mathrm{initial}} = 0.0526$, $F_{50\,\mathrm{standard}} = 0.0359$.

The effect of the Bohr shift correction is also demonstrated in figure 2; line A is without any correction, and line B is corrected for the increasing $Fa_{\mathrm{CO_2}}$ throughout the apnoea. This correction is applied thereafter to all curves illustrating the model. Line C represents apnoea with an elevated initial $Fa_{\mathrm{CO_2}}$.

The effects of alterations in physiological variables on the rate of arterial oxyhaemoglobin desaturation are demonstrated in figure 3. The effect of different alveolar volumes is shown in figure 3A. The volumes shown represent alveolar volume at: total lung capacity (6.0 litre), resting expiratory level (2.5 litre) and supine resting expiratory level after anaesthesia (2.0 litre) [6]. The effects of $F\mathrm{A}_{\mathrm{O_2}\,\mathrm{initial}}$ on the subsequent rate of oxyhaemoglobin desaturation is shown in figure 3B. These values were chosen to represent normality ($F\mathrm{A}_{\mathrm{O_2}\,\mathrm{initial}} = 0.133$) and pre-apnoea hypoventilation ($F\mathrm{A}_{\mathrm{O_2}\,\mathrm{initial}} = 0.1$). The effect of shunt is shown in figure 3C, the nominal values being 0%, 5%, 10% and 15% of $\dot{Q}\mathrm{T}$. The effect of variation in oxygen consumption rate (metabolic rate) is shown in figure 3D. The effect of alterations in the total oxygen carrying capacity of the blood is shown in figure 3E and F. This has been separated into the effects of anaemia (3E) and hypovolaemia (3F).

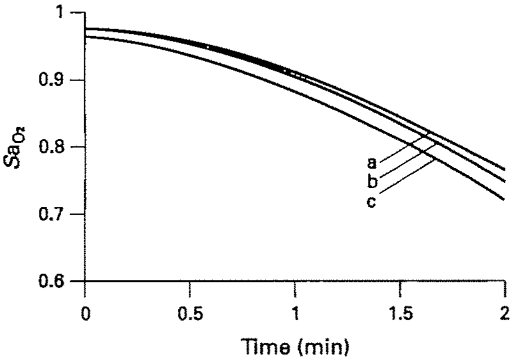


Figure 2 Effect of the Bohr shift on the time course of $Sa_{\mathrm{O_2}}$ in apnoea. a: ignoring the effect of the Bohr shift; b: implementing the dynamic Bohr shift within the same apnoea as above. This is the "standard adult" curve; c: implementing the dynamic Bohr shift during an apnoea with an elevated initial $F\mathrm{A}_{\mathrm{O_2}}$ (0.08).

SPECIFIC CLINICAL SCENARIOS

The model was used to predict the consequences of various clinical abnormalities on the time course of arterial oxyhaemoglobin desaturation during apnoea. The data for these examples are given in table 1.

Figure 4 shows theoretical plots for a standard adult, and 20-kg and 10-kg infants. A theoretical plot for a typical obese adult was constructed and is shown in figure 5. Figure 5 also shows the theoretical plot for a normal adult in the postoperative period after major surgery.

We have calculated the apnoea time required to reduce the oxyhaemoglobin saturation to 85% for a standard adult, a standard 10-kg infant and an obese adult both with and without preoxygenation (table 2). Preoxygenation, if resulting in complete nitrogen washout, is assumed to result in an $F\mathrm{A}_{\mathrm{O_2}\,\mathrm{initial}}$ of 0.87 ($P\mathrm{B}$dry = 93.7 kPa, $P\mathrm{A}_{\mathrm{CO_2}}$ = 5.3 kPa and r = 0.8).

Discussion

We have described a model of oxyhaemoglobin desaturation in the apnoeic patient. All major variables in this model, namely $V\mathrm{A}$, $F\mathrm{A}_{\mathrm{O_2}\,\mathrm{initial}}$, $\dot{V}\mathrm{O_2}$, $Q\mathrm{T}$, shunt and total oxygen carrying capacity, may be expected to change in the perioperative period.

The alveolar volume at the onset of apnoea is an important determinant of the rate of oxyhaemoglobin desaturation because this is a large store of oxygen. As $F\mathrm{A}_{\mathrm{O_2}}$ is only 0.133 at an $F\mathrm{I}_{\mathrm{O_2}}$ of 0.21, changes in alveolar volume have a limited effect at this $F\mathrm{I}_{\mathrm{O_2}}$. The effect of reduced alveolar volume is more marked when $F\mathrm{A}_{\mathrm{O_2}}$ is higher, for example after preoxygenation (see below). The rate of oxyhaemoglobin desaturation was found to be very sensitive to changes in initial $F\mathrm{A}_{\mathrm{O_2}}$ with a reduction from 0.133 to 0.1, resulting in a shortening of the apnoea time required to reduce the oxyhaemoglobin saturation to 85% from 84 to 60 s. A reduction in initial $F\mathrm{A}_{\mathrm{O_2}}$ may occur with both hypoventilation and low mean $\dot{V}/\dot{Q}$, both of which increase $F\mathrm{I}_{\mathrm{O_2}} - F\mathrm{A}_{\mathrm{O_2}}$. Roe and Jones [9] have described low values of $Sp_{\mathrm{O_2}}$ (with $F\mathrm{I}_{\mathrm{O_2}} = 0.21$) in the postoperative period which returned to normal with an $F\mathrm{I}_{\mathrm{O_2}}$ value of 0.4. This would correspond to the behaviour predicted from their model [10] of the relationship between $F\mathrm{I}_{\mathrm{O_2}}$ and $Sa_{\mathrm{O_2}}$ in the presence of hypoventilation or low mean $\dot{V}/\dot{Q}$, suggesting that these patients may have had a low $F\mathrm{A}_{\mathrm{O_2}}$ value. It is of interest that these patients were also noted to have an unstable pattern of $Sp_{\mathrm{O_2}}$ at an $F\mathrm{I}_{\mathrm{O_2}}$ of 0.21. This is in accordance with the model described here where a low $F\mathrm{A}_{\mathrm{O_2}}$ value is associated with a greater propensity for oxyhaemoglobin desaturation.

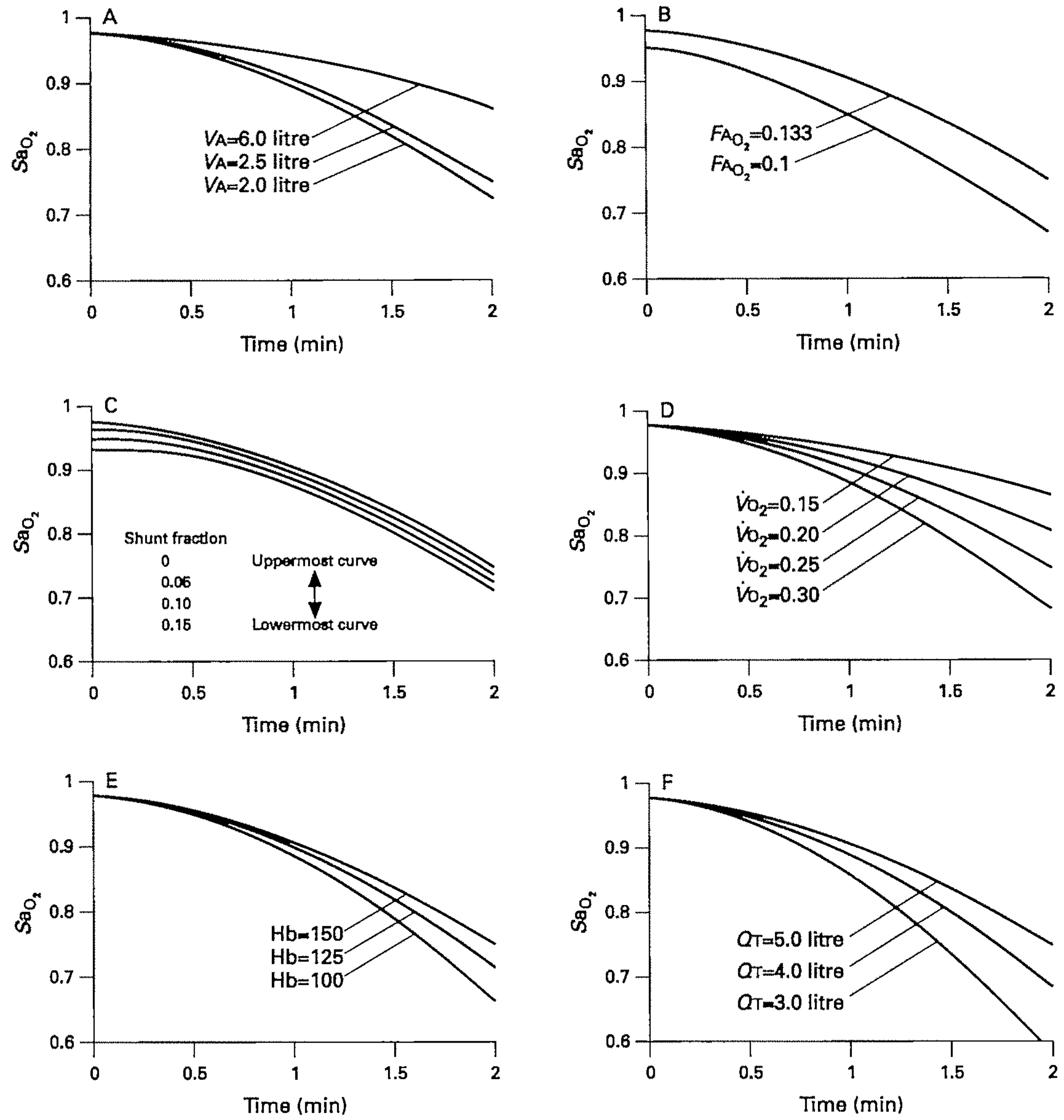


*Figure 3*A Effect of lung volume (*V*A litre) on the time course of Sa_{O_2} in apnoea. B: Effect of initial FA_{O_2} on the time course of Sa_{O_2} in apnoea. C: Effect of shunt fraction (f_s) ranging from 0 to 15% on the time course of Sa_{O_2} in apnoea. D: Effect of oxygen consumption rate ($\dot{V}O_2$) ranging from 0.15 to 0.3 litre min^{-1} on the time course of Sa_{O_2} in apnoea. E: Effect of haemoglobin concentration (Hb g $litre^{-1}$) on the time course of Sa_{O_2} in apnoea. F: Effect of total blood volume (*Q*T) on the time course of Sa_{O_2} in apnoea.

Table 1 Examples of data used in the model to predict the consequences of various clinical abnormalities on the time course of arterial oxyhaemoglobin desaturation during apnoea (see text for details)

Body weight (kg)	Approx. age (yr)	Surface area (m^2)	Hb (g $litre^{-1}$)	Blood volume (litre)	Cardiac output (litre min^{-1})	Alveolar volume (litre)	$\dot{V}O_2$ (litre min^{-1})	Shunt fraction	$FA_{O_2 initial}$	$FA_{CO_2 initial}$
10	1	0.44	100	0.84	1.12	0.22	0.056	0	0.133	0.0526
20	5	0.775	120	1.55	2.00	0.68	0.095	0	0.133	0.0526
70 standard	—	1.85	150	5.00	5.00	2.5	0.250	0	0.133	0.0526
70 postop.	—	1.85	100	4.00	4.00	2.0	0.250	0.1	0.100	0.08
127 obese	—	2.41	150	6.16	7.56	1.0	0.378	0	0.133	0.0526
Reference	—	[7]	—	[7]	[7]	[6, 8]	[7]	—	—	—

A spread of $\dot{V}/\dot{Q}$ mismatch (increased $\log_{SD} \dot{Q}$) has a complex effect involving a number of different compartments, contributing according to their size [10]. The effects of both reduced $FA_{O_2 initial}$ and reduced *V*A are combined in each compartment. The effect of spread of $\dot{V}/\dot{Q}$ ratios, as distinct from a reduction in mean $\dot{V}/\dot{Q}$, has not been modelled. However, the effect of mean $\dot{V}/\dot{Q}$ on $FA_{O_2 initial}$ is by far the most important effect of ventilation perfusion mismatch. A dispersion of $\dot{V}/\dot{Q}$ ratio about this mean results in some compartments (low $\dot{V}/\dot{Q}$) contributing to desaturation before others (high

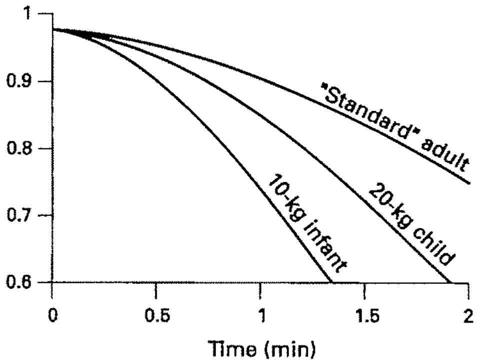


Figure 4 Time course of Sa_{O_2} in apnoea in children compared wih the standard adult.

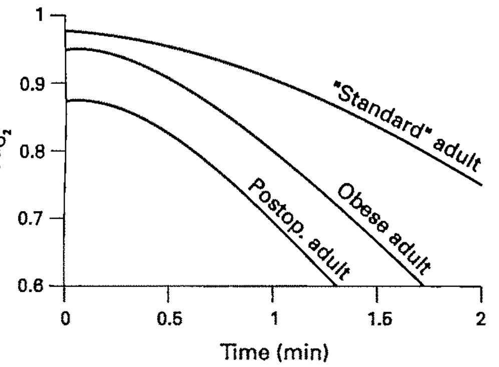


Figure 5 Time course of Sa_{O_2} in apnoea in obesity and in a "typical" postoperative patient compared with the standard adult (see text).

Table 2 Apnoea time required to reduce oxyhaemoglobin saturation (Sa_{O_2}) to 85 % for a standard adult, standard 10-kg infant and obese adult, both with and without preoxygenation

	Time (s) to $Sa_{O_2} = 0.85$	
	$FA_{O_2,\text{initial}} = 0.133$	$FA_{O_2,\text{initial}} = 0.87$
Standard adult (70 kg)	84	502
Standard infant (10 kg)	41	180
Obese adult (127 kg)	46	171

$\dot{V}/\dot{Q}$), thereby to a certain extent cancelling each other out. An important exception is where there is a large contribution from an area of lung with very low $\dot{V}/\dot{Q}$. In this case the desaturation curve is determined, albeit in part, by the processes illustrated in figure 3B, resulting in a faster initial rate of desaturation. It is important to distinguish this effect from that of true shunt where the initial saturation but not rate of desaturation is altered (fig. 3C).

True shunt, measured by multiple inert gas elimination, increases during anaesthesia and this abnormality may persist for some time into the postoperative period. The effect of varying the shunt on the model is shown in figure 3C. It is evident from equation (4) that if a shunt exists, the arterial oxyhaemoglobin saturation is dependent on cardiac output. However, if the shunt fraction is zero, then arterial oxyhaemoglobin saturation is independent of cardiac output.

All physiological models have limitations. The model described here overcomes the serious deficiency of earlier models by taking account of the fact that apnoea is not a steady state situation. However, there are several assumptions that we have made in our model. We have assumed that alveolar gas is completely mixed at all times and is all immediately available for gas exchange. We have ignored the small change in lung volume which occurs when oxygen and carbon dioxide are exchanged with a respiratory quotient less than 1. We have assumed that cardiac output and $\dot{V}O_2$ remain unchanged during apnoea, although it is important to note that both of these variables may increase during the course of an obstructive apnoea. We assume that the circulation behaves as a single unit with a given mean transit time and with no mixing of blood. In the true situation, there is a spread of circulation transit time values as a result of the variation in blood circulation path lengths. In addition, mixing of blood occurs because of the distribution of velocities in laminar flow.

Oxygen consumption is commonly taken to be 0.25 litre min^{-1} although during anaesthesia a value in the region of 0.20 litre min^{-1} is more likely [11]. Delauney, Bonnet and Duvaldestin [12] studied $\dot{V}O_2$ in patients in the postoperative period and found values of approximately 0.15 litre min^{-1}, although this was increased by 40 % in patients who were shivering. Catabolic patients and patients with malignant hyperpyrexia have considerably increased $\dot{V}O_2$ values and desaturate at a much greater rate. Fletcher and colleagues [13] have shown an increased $\dot{V}O_2$ during obstructive apnoea. Increased metabolic rate associated with an increased $\dot{V}O_2$ value is also associated with increased $\dot{V}CO_2$. This alters the Bohr shift effect and has been incorporated in the construction of figure 3D (just as all plots are correct for Bohr shift) by assuming that $\dot{V}CO_2 = 0.8\ \dot{V}O_2$. A wide range of oxygen consumption is clearly possible and figure 3D shows the effect that this would have on the rate of oxyhaemoglobin desaturation.

The oxygen content of the blood, approximately 0.8 litre, might be expected to act as a "buffer" which moderates the rate of oxyhaemoglobin desaturation as oxygen is consumed from this compartment during apnoea. The total oxygen capacity of the blood is seen to be an important determinant of the rate of arterial oxyhaemoglobin desaturation in our model. This has been divided into consideration of the effects of anaemia (fig. 3E) and hypovolaemia (fig. 3F) because despite having common mechanisms within the model, they may be separate clinical entities. It should also be noted that fractional decrements in either have a multiplicative and not additive effect on the rate of arterial oxyhaemoglobin desaturation.

$S\bar{v}_{O_2}$ is not an independent variable determining the rate of desaturation but is linked through coupling with other variables. In the single apnoea, pre-apnoeic $S\bar{v}_{O_2}$ is lowered by either an increased oxygen consumption rate or a reduced cardiac output.

We have not incorporated into the model the effect of nitrous oxide elimination. Lampe and colleagues

[14] found that when nitrous oxide was added to isoflurane it failed to increase the incidence of early or late postoperative hypoxaemia compared with only oxygen and isoflurane. However, Einarsson and his co-workers [15] found reduced oxyhaemoglobin saturation after nitrous oxide anaesthesia in hypoventilating patients even when $F\text{I}_{O_2}$ was 0.3. As none of their desaturations was < 90%, diffusion hypoxia is probably an unimportant cause of postoperative hypoxaemia.

In both paediatric examples, an arterial oxyhaemoglobin saturation of 85% was reached after a considerably reduced apnoea time; 41 and 60 s, respectively, compared with 84 s in a standard adult. These reduced apnoea times were largely the result of a relatively high $\dot{V}O_2$ and a relatively low alveolar volume with respect to weight, compared with the standard adult (see table 1). In addition, despite the greater relative total blood volume, the "buffering capacity" of the blood oxygen store was reduced as a result of the low haemoglobin concentration.

In the example of a morbidly obese patient, an oxyhaemoglobin saturation of 85% was reached after 46 s (fig. 5). This was largely the result of a much decreased alveolar volume compared with a standard adult (see table 1). In addition, a lesser relative blood volume reduces the buffering capacity of the body oxygen stores.

The effect of preoxygenation on the time to Sa_{O_2} of 85% in a normal adult, a 10-kg infant and an obese adult (127 kg) is shown in table 2. Effective preoxygenation in a standard adult results in a time to Sa_{O_2} = 85% of 502 s. This is reduced to 180 s in the 10-kg infant and 171 s in the morbidly obese. This model result in the morbidly obese example is in agreement with the experimental data of Berthoud, Peacock and Reilly [16]. The reduced benefit of preoxygenation in the morbidly obese is a result of the very low alveolar volume which represents the only potentially increasable oxygen store in the body. The oxygen storage capacity of blood (as oxyhaemoglobin) has little capacity for any increase as a result of the shape of the oxyhaemoglobin dissociation curve.

The typical postoperative scenario (fig. 5) is to some extent a "worst case" example in that the effect of hypovolaemia, reduced cardiac output, anaemia, increased $\dot{V}/\dot{Q}$ mismatch, increased shunt, pre-apnoea hypoventilation and reduced alveolar volume are included. However, the values of these abnormalities individually are by no means excessive and each could easily occur in the postoperative period. It is important to appreciate that such abnormalities could occur in a variety of combinations and that some may be considerably more impaired than in this example. What is particularly interesting here is the marked rate of oxyhaemoglobin desaturation that occurs as a result of a combination of small abnormalities. The relative importance of abnormalities in these variables may be seen individually in figure 3. The initial oxyhaemoglobin saturation of 88.5% ($F\text{I}_{O_2}$ 0.21) is not uncommon in the early postoperative period. The short time (23 s) for this patient's oxyhaemoglobin saturation to reduce to 85% demonstrates the seriousness of apnoea in the postoperative patient where the initial oxyhaemoglobin saturation is reduced and the rate of oxyhaemoglobin desaturation from that level is increased. Here, relatively short periods of obstruction or apnoea lead to significant desaturations.

There has been some discussion as to whether or not oxyhaemoglobin desaturation is faster in obstructive rather than central apnoea. Strohl and Altose [17], however, found no difference in the rate of oxyhaemoglobin desaturation between simulated apnoea and obstruction in healthy subjects. Fletcher and co-workers [18], in an animal study, found a greater rate of oxyhaemoglobin desaturation during obstruction than during apnoea with paralysis. This difference was shown to be a result of increased $\dot{V}O_2$ in non-paralysed spontaneously ventilating but artificially obstructed animals. This increase in the rate of oxyhaemoglobin desaturation with increased $\dot{V}O_2$ is predicted by our model and is shown in figure 3D.

In summary, we have presented a model to describe the time course of oxyhaemoglobin desaturation during apnoea which illustrates the effect and interaction of various pathophysiological abnormalities which may occur. Insights gained from this model will be useful in understanding preoxygenation, postoperative hypoxaemia and sleep apnoea.

Appendix

A SIMPLE EXPRESSION FOR THE OXYHAEMOGLOBIN DISSOCIATION CURVE

End-capillary oxyhaemoglobin saturation can be expressed in terms of the alveolar oxygen fraction using this variation of the Hill equation [19, 20]. It is sufficiently accurate for the purposes of this model.

$$Sc' = b \times \left(\frac{F\text{A}_{O_2}{}^{n}}{F_{50}{}^{n} + F\text{A}_{O_2}{}^{n}} \right)$$

where $b = 0.998$, $n = 2.937$, $F_{50} = 0.0359$.

Acknowledgement

We thank Professor W. W. Mapleson for his assistance with this article.

References

1. Findley LJ, Ries AL, Tisi GM, Wagner PD. Hypoxemia during apnea in normal subjects: mechanisms and impact of lung volume. *Journal of Applied Physiology* 1983; 55: 1777–1783.
2. Kelman RG. Digital compouter subroutine for the conversion of oxygen tension into saturation. *Journal of Applied Physiology* 1966; **21**: 1375–1376.
3. Adams AP, Hahn CEW. *Principles and Practice of Blood Gas Analysis*, 2nd Edn. Edinburgh: Churchill Livingstone, 1982; 45.
4. Nunn JF. *Applied Respiratory Physiology*, 3rd Edn. Oxford: Butterworths, 1987; 226.
5. McHardy GJR. The relationship between differences in pressure and content of carbon dioxide in arterial and venous blood. *Clinical Science* 1967; **32**: 299–309.
6. Damia G, Mascheroni D, Croci M, Tarenzi L. Preoperative changes in functional residual capacity in morbidly obese patients. *British Journal of Anaesthesia* 1988; **60**: 574–578.
7. Lentner C, ed. *Geigy Scientific Tables, vol. 5*. Ciba-Geigy, 1990; 46, 102, 103, 105.

8. Crone RK, O'Rourke PP. Pediatric and neonatal intensive care. In: Miller RD, ed. *Anesthesia*, 3rd Edn. Edinburgh: Churchill Livingstone, 1990; 2211–2275.
9. Roe PG, Jones JG. Causes of oxyhaemoglobin saturation instability in the postoperative period. *British Journal of Anaesthesia* 1993; 71: 481–487.
10. Roe PG, Jones JG. Analysis of factors which affect the relationship between inspired oxygen partial pressure and arterial oxygen saturation. *British Journal of Anaesthesia* 1993; 71: 488–494.
11. Nunn JF. *Applied Respiratory Physiology*, 3rd Edn. Oxford: Butterworths, 1987; 366.
12. Delauney L, Bonnet F, Duvaldestin P. Clonidine decreases postoperative oxygen consumption in patients recovering from general anaesthesia. *British Journal of Anaesthesia* 1991; 67: 397–401.
13. Fletcher EC, Goodnight-White S, Munafo D, Miller CC III, Lucket C, Qian W. Rate of oxyhemoglobin desaturation in obstructive versus nonobstructive apnea. *American Review of Respiratory Disease* 1991; **143**: 657–660.
14. Lampe GH, Wauk LZ, Whitendale P, Way WL, Kozmary SU, Daneghan JH, Eger EI II. Postoperative hypoxemia after non-abdominal surgery: A frequent event not caused by nitrous oxide. *Anesthesia and Analgesia* 1990; 71: 597–601.
15. Einarsson S, Stenqvist O, Bengtsson A, Houltz E, Bengtson JP. Nitrous oxide elimination and diffusion hypoxia during normo- and hypoventilation. *British Journal of Anaesthesia* 1993; 71: 189–193.
16. Berthoud MC, Peacock JE, Reilly CS. Effectiveness of preoxygenation in morbidly obese patients. *British Journal of Anaesthesia* 1991; 67: 464–466.
17. Strohl KP, Altose MD. Oxygen saturation during breath-holding and during apneas in sleep. *Chest* 1984; 85: 181–186.
18. Fletcher EC, Kass R, Thornby JI, Rosborough J, Miller T. Central venous oxygen saturation and rate of arterial desaturation during obstructive apnoea. *Journal of Applied Physiology* 1989; **66**: 1477–1485.
19. Hill AV. The possible effect of the aggregation of the molecules of haemoglobin on its dissociation curve. *Journal of Physiology (London)* 1910; **40**: iv–vii.
20. Stryer L. *Biochemistry*, 2nd Edn. San Francisco: WH Freeman & Co, 1981; 65–68.

British Journal of Anaesthesia 1996; **76**: 292–296

Nitrous oxide and the rate of gas uptake from an unventilated lung in dogs

C. J. JOYCE, A. B. BAKER, R. PARKINSON AND M. ZACHARIAS

Summary

We have studied the effect of $F_{I_{O_2}}$ of a nitrous oxide–oxygen mixture on the rate of gas uptake from an unventilated lung. Nine anaesthetized dogs were studied, each breathing four nitrous oxide–oxygen mixtures ($F_{I_{O_2}}$ 0.3, 0.5, 0.75 and 1.0) in random order. A double-lumen endobronchial tube separated lung ventilation. Both lungs were given the nitrous oxide–oxygen mixture for an equilibration period. Then the right lung was connected to a spirometer containing the same gas, and gas uptake measured. In every dog, gas uptake was faster with an $F_{I_{O_2}}$ of 0.5 or 0.75 than with an $F_{I_{O_2}}$ of 1.0. When breathing a nitrous oxide–oxygen mixture with $F_{I_{O_2}} > 0.3$, the rate of gas uptake from the unventilated lung was faster than with 100% oxygen. (*Br. J. Anaesth.* 1996; **76**: 292–296)

Key words

Anaesthetics gases, nitrous oxide. Lung, gas exchange. Oxygen, inspired concentration. Dog.

Pulmonary collapse is a common clinical problem after upper abdominal [1] and thoracic operations [2]. One of the proposed mechanisms of perioperative pulmonary collapse is absorption atelectasis [3]. Absorption atelectasis occurs when the net rate of gas transfer from the lung unit into the blood exceeds the rate of gas delivery into a lung unit by inspired ventilation. This may occur when gas is trapped behind closed airways and there is no ventilation to the corresponding lung unit [3, 4], although complete airway closure is not necessary [5, 6].

The rate of gas absorption from an unventilated area of lung depends on the inspired gas composition [7–10]. $F_{I_{O_2}}$ and the solubility of any inert gas in the inspired mixture are important determinants of the rate of gas absorption. If the inspired mixture contains a relatively insoluble gas such as nitrogen, the rate of gas uptake is relatively slow and increases as $F_{I_{O_2}}$ increases [9, 11]. When the inspired gas contains oxygen and a relatively soluble inert gas, gas uptake is faster. While nitrous oxide is less soluble than the volatile anaesthetic gases, in physiological terms nitrous oxide is highly soluble. Theoretical models predict that under some conditions an unventilated area of lung collapses more rapidly when breathing a nitrous oxide–oxygen mixture than when breathing 100% oxygen [9, 12].

Conditions that favour the development of absorption atelectasis exist during anaesthesia. Lung volume is reduced [13–22] and airways closure may occur [14, 23, 24], particularly in middle-aged or elderly patients [23]. Nitrous oxide–oxygen mixtures are commonly used as the inspired gas.

Dale and Rahn developed a dog preparation that measures the rate of gas uptake and the changes in gas composition within a lung, when ventilation to that lung ceases [8]. We used this preparation to examine gas uptake from an unventilated lung, when breathing nitrous oxide–oxygen mixtures with a range of $F_{I_{O_2}}$ values.

Materials and methods

Ethics approval for this study was obtained from the University of Otago Animal Ethics Committee. We studied nine healthy mongrel dogs (weights 18–39 kg). Anaesthesia was induced with i.v. thiopentone and maintained with a thiopentone infusion. After oral tracheal intubation, a femoral artery catheter and a Swan-Ganz pulmonary artery catheter were inserted. Spontaneous breathing was maintained throughout the experiment. Pulmonary arterial pressure, femoral arterial pressure and end-tidal carbon dioxide concentration were monitored continuously. Surgical tracheotomy was performed and a Rüsch double-lumen endobronchial tube for dogs inserted. The cuff of the endobronchial tube was inflated with 10 ml of water and the tube secured. Functional isolation of the lungs and patency of the endobronchial tube lumens were tested. When correct placement of the endobronchial tube was confirmed, breathing of the selected gas mixture began. A diagram of the breathing circuit and an explanation of its function are given in figure 1. In this preparation the right lung is not truly unventilated, but rather rebreathing from a small volume closed system with no fresh gas flow.

On each occasion both lungs breathed the test gas for at least 1 h to allow equilibration (tap A in "breathing circuit position"). End-tidal carbon dioxide was maintained at 5.3–8.6 kPa by adjusting the rate of thiopentone infusion. The spirometer was filled with the same test gas to a volume of 1000 ml

---

C. J. JOYCE, MB, CHB, PHD, FANZCA, Department of Intensive Care, Royal Melbourne Hospital, Melbourne, Australia. A. B. BAKER, MB, BS, DPHIL, FANZCA, FRCA, Department of Anaesthetics, University of Sydney, Royal Prince Alfred Hospital, Sydney, Australia. R. PARKINSON, BSC, BA, DIPGRAD, M. ZACHARIAS, FRCA, FANZCA, MS, PHD, Department of Anaesthesia and Intensive Care, University of Otago Medical School, Dunedin, New Zealand.

Accepted for publication: September 21, 1995.

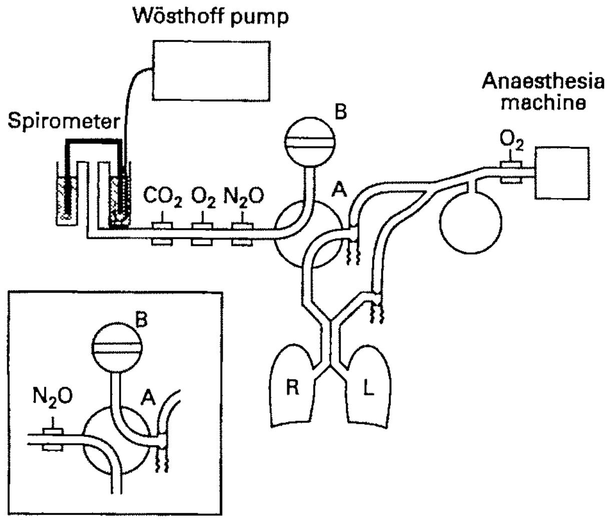


Figure 1 The breathing circuit. The main diagram shows the breathing circuit with tap A in the "breathing circuit position". Both lungs inhale from the reservoir bag, and exhale to atmosphere via one-way valves and reservoir tubing. Each lung ventilates through a separate non-rebreathing valve. The spirometer can be flushed out and filled with gas as desired, with tap B controlling whether the spirometer is open to atmosphere or sealed. When required for flushing or filling, gas of the desired composition was pumped into the spirometer from the Wösthoff pump via fine-bore tubing which was removed at the end of filling. "O_2", "CO_2" and "N_2O" are inline gas analysers. The insert shows the breathing circuit with tap A in the "spirometer position". The right lung is connected to the spirometer from which it rebreathes via the right endobronchial tube. The left lung continues to breathe gas from the reservoir bag as before.

above the bottom of its range. Recordings of arterial pressure, pulmonary artery pressure, spirometer volume and gas composition (partial pressures of oxygen, nitrous oxide and carbon dioxide) were started. At the end of an inspiration, tap A was turned to the "spirometer position", so that the right lung began to rebreathe from the spirometer, while the left lung continued to breathe test gas as before. Recordings were continued until the spirometer began to hit the stop at the bottom of its range. Just before this point was reached, mixed venous blood-gas samples were obtained. At the end of the recording, isolation of the lungs and patency of the lumens of the endobronchial tube were rechecked, then breathing of both lungs on the next test gas started.

All gas analysers in this experiment were "inline" and did not remove gas from the circuit. Instruments used were: oxygen analysis—Teledyne TED 100 polarographic oxygen analyser; nitrous oxide analysis—Dräger Irina anaesthetics measuring instrument analyser; and carbon dioxide analysis—Hewlett Packard 47210A CO_2 analyser with HP14360A carbon dioxide transducer. Blood gases were measured with a Radiometer ABL300 acid–base laboratory. A Krogh spirometer was used. The dead-space of the spirometer circuit including spirometer residual volume at the bottom stop, connecting tubing and the endobronchial tube, was 340 ml.

For each dog, recordings were made with four test gas mixtures. These were combinations of nitrous oxide and oxygen with F_{IO_2} values of 0.3, 0.5, 0.75 and 1.0, which were given in random order. When the recordings were analysed, observations of the pattern of composition and volume changes were made. The volume that 950 ml BTPS (37 °C, 760 Torr) would occupy at ambient temperature (ATPS) was calculated. The time for the spirometer volume at end-expiration to decrease by this amount (T_{950}) was measured: 950 ml BTPS was selected as the largest volume that could be measured from all the traces, before the spirometer began to hit the stop at the bottom of its range. P_{O_2} and the P_{CO_2} in the spirometer were recorded continuously, and noted at the time mixed venous P_{O_2} and P_{CO_2} were measured.

At the end of each study, after the nitrous oxide–oxygen recordings had been completed, eight of the dogs breathed 100% oxygen for at least 1 h, then recordings were made while the left lung continued to breathe 100% oxygen and the right lung rebreathed from the spirometer that had been filled with air (oxygen:air experiment). The rate of uptake from the spirometer when a state of constant composition within the spirometer had been reached and the uptake had stabilized was measured for F_{IO_2} 1.0 and the oxygen:air experiments. This allowed validation of the technique, by comparison with Dale and Rahn's results from a similar preparation [8]. This part of the experiment was not conducted on one of the nine dogs, because of time constraints on laboratory availability on the day that dog was studied.

The effect of F_{IO_2} on T_{950} was analysed using repeated measures analysis of variance. *Post hoc* testing was performed with both Fisher's PLSD (protected least significant difference) and Scheffé tests [25, 26]. These analyses were performed with Statview II version 1.04 using a Macintosh Centris 650.

Results

The results for T_{950} are presented in table 1 and figure 2. Repeated measures analysis of variance demonstrated a highly significant within-subjects difference between the results for the four gas compositions ($P = 0.0001$). Results of multiple comparison testing between the different gas com-

Table 1 Time (s) for end-expiratory volume in the spirometer to decrease by 950 ml BTPS (T_{950}), breathing different nitrous oxide–oxygen mixtures. Residual sum of squares = 9485. Standard error of the difference between two treatment means = 46

	F_{IO_2}			
	0.3	0.5	0.75	1.0
Dog 1	656	391	499	669
Dog 2	651	602	570	618
Dog 3	462	279	382	467
Dog 4	787	682	827	1353
Dog 5	349	414	395	575
Dog 6	749	638	557	760
Dog 7	731	509	573	777
Dog 8	895	699	858	983
Dog 9	1011	764	854	1112
Mean	699	553	613	813

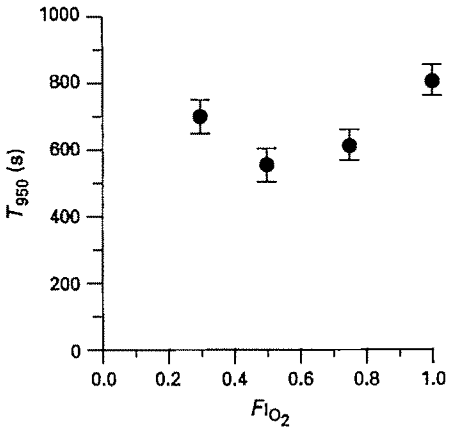


Figure 2 T_{950} for $F\text{I}_{O_2}$ 0.3, 0.5, 0.75 and 1.0. The error bars are SE of the difference between treatment means (each $F\text{I}_{O_2}$ is a treatment). Compare with the relationship between "time to collapse" and $F\text{I}_{O_2}$ predicted by the mathematical model (fig. 4).

Table 2 Results of multiple comparison tests between T_{950} recorded with different $F\text{I}_{O_2}$ values

Comparison	Fisher PLSD	Scheffé
0.3–0.5	$0.001 < P < 0.01$	$0.01 < P < 0.05$
0.3–0.75	ns	ns
0.3–1.0	$0.01 < P < 0.05$	ns
0.5–0.75	ns	ns
0.5–1.0	$P < 0.001$	$P < 0.001$
0.75–1.0	$P < 0.001$	$0.001 < P < 0.01$

positions, with Fisher's PLSD and Scheffé tests, are presented in table 2. When $F\text{I}_{O_2}$ was greater than 0.3, the rate of gas uptake from the unventilated lung was faster than when $F\text{I}_{O_2}$ was 1.0.

The changes in gas composition in the spirometer depended on $F\text{I}_{O_2}$ (see fig. 3, table 3). With all $F\text{I}_{O_2}$ values, $P\text{CO}_2$ increased and stabilized slightly above $P\bar{v}_{CO_2}$. With an $F\text{I}_{O_2}$ of 0.3, $P\text{O}_2$ decreased to stabilize at a level slightly above $P\bar{v}_{O_2}$, and $P\text{N}_2\text{O}$ increased and stabilized. With an $F\text{I}_{O_2}$ of 0.5 or 0.75, $P\text{O}_2$ decreased linearly and $P\text{N}_2\text{O}$ increased linearly, with neither showing signs of stabilizing. With an $F\text{I}_{O_2}$ of 1.0, $P\text{O}_2$ decreased, then stabilized as $P\text{CO}_2$ stabilized. With $F\text{I}_{O_2}$ values of 0.5, 0.75 and 1.0, $P\text{O}_2$ in the spirometer was substantially higher than $P\bar{v}_{O_2}$.

Table 3 $P\bar{v}_{O_2}$ and $P\bar{v}_{CO_2}$ (kPa) measured just before the spirometer hit the bottom stop, and $P\text{O}_2$ and $P\text{CO}_2$ (kPa) in the spirometer at that time. Values are mean (SD) [range]

	$F\text{I}_{O_2}$			
	0.3	0.5	0.75	1.0
$P\bar{v}_{O_2}$	5.6 (1.2) [3.1–7.1]	7.6 (0.9) [6.0–8.8]	8.8 (1.1) [7.6–10.3]	9.1 (1.3) [7.3–11.9]
$P\text{O}_2$	8.0 (0.7) [6.9–9.1]	27.5 (1.9) [24.8–29.9]	55.7 (3.2) [49.7–60.0]	81.6 (3.5) [76.4–87.2]
$P\bar{v}_{CO_2}$	8.1 (1.3) [6.1–9.6]	8.9 (1.3) [6.8–10.9]	9.7 (1.2) [7.6–11.3]	9.5 (1.3) [7.3–11.7]
$P\text{CO}_2$	9.3 (1.3) [6.8–10.9]	10.4 (1.3) [8.5–11.7]	10.9 (1.1) [9.5–12.4]	11.1 (1.6) [8.5–13.7]

Table 4 Rate of uptake during constant composition in the $F\text{I}_{O_2}$ 1.0 and oxygen:air experiments (eight dogs). Presented as ml_{ATPS} min^{-1} kg^{-1} to allow comparison with Dale and Rahn's results (see discussion). Ratio of rate of uptake in $F\text{I}_{O_2}$ 1.0 experiment/rate of uptake in oxygen:air experiment, during constant composition, is also given

$F\text{I}_{O_2}$ 1.0	Oxygen:air	$F\text{I}_{O_2}$ 1.0/oxygen:air
5.64	0.644	8.76
4.90	0.370	13.23
2.49	0.554	4.50
4.35	0.643	6.77
3.28	0.280	11.70
3.25	0.187	17.38
3.23	0.314	10.29
3.12	0.493	6.33

A state of constant composition was reached during $F\text{I}_{O_2}$ 1.0 and the oxygen:air experiments. The ratio (rate of uptake during constant composition with $F\text{I}_{O_2}$ 1.0:rate of uptake during constant composition with oxygen:air) was calculated for individual dogs from our data (see table 4). These results (mean 9.87) were not significantly different ($P > 0.05$, one sample t test) from Dale and Rahn's mean value of 9.17 [8], supporting the validity of our experimental technique.

Discussion

When ventilation to a lung unit ceases, the rate of gas uptake from that lung unit by the blood determines the rate at which absorption atelectasis develops. We

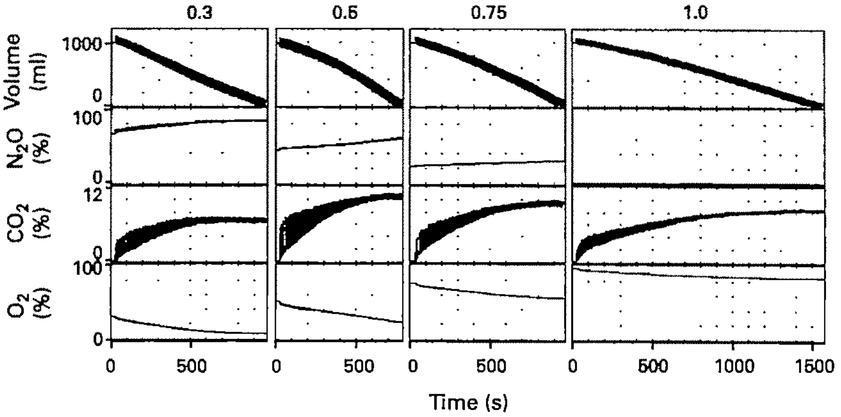


Figure 3 Volume and composition changes in the spirometer. Typical pattern of volume and composition changes in the spirometer. The recordings from one dog are shown for the four different $F\text{I}_{O_2}$ values.

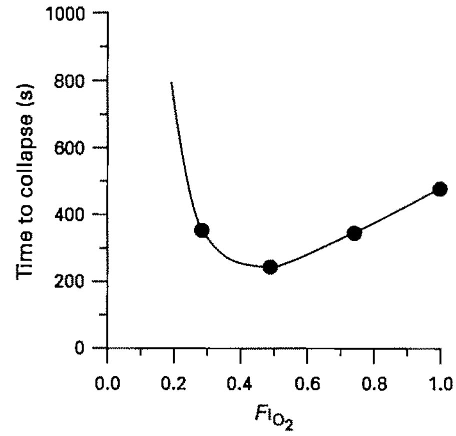


Figure 4 Predictions of mathematical model. A mathematical model [9] was used to predict time to collapse of a lung unit to which the airway becomes occluded while breathing different nitrous oxide–oxygen mixtures. Points on the line are predictions at the $F_{I_{O_2}}$ studied with the experimental preparation.

used a dog preparation to measure the rate of gas uptake and changes in gas composition within a lung, when ventilation to that lung ceased while breathing nitrous oxide–oxygen mixtures. It was found that the rate of gas uptake depended on $F_{I_{O_2}}$. When $F_{I_{O_2}}$ was greater than 0.3, the rate of gas uptake was faster than when $F_{I_{O_2}}$ was 1.0.

An area of non-ventilated lung, such as a lung or a pulmonary lobe with an occluded bronchus, or an alveolus with an occluded airway, behaves as a closed collapsible cavity with perfusion limitation [8, 9, 27, 28]. Most of the proposed methods of modelling gas uptake from closed collapsible cavities [29–31] have assumed that the oxygen and carbon dioxide in the cavity equilibrate instantaneously with venous blood. With our experimental preparation, P_{CO_2} in the spirometer approached $P\bar{v}_{CO_2}$ rapidly, but P_{O_2} in the spirometer did not always rapidly approach $P\bar{v}_{O_2}$ (see fig. 3, table 3). This demonstrates that when modelling gas uptake from an unventilated lung unit, it is reasonable to assume that equilibration is instantaneous for carbon dioxide, but this assumption is not valid for oxygen when breathing nitrous oxide–oxygen mixtures. This is in keeping with the prediction of mathematical models [9], that assuming instantaneous equilibration of oxygen introduces considerable inaccuracy. A mathematical model that made no such assumptions about equilibration rates [9] was used to calculate the time taken for an unventilated lung unit to collapse when breathing nitrous oxide–oxygen mixtures with a range of $F_{I_{O_2}}$ values. The results of these calculations are presented in figure 4. The absolute times depend on the initial volume of the lung unit and the blood flow to the lung unit, but the ratio (time to collapse with gas mixture A: time to collapse with gas mixture B) is independent of these factors. If this is taken into account there is a striking similarity in the pattern of results for T_{950} presented in figure 2, despite differences between the model and the experimental preparation.

P_{CO_2} in the spirometer initially increases because of mixing with alveolar gas, transfer of carbon dioxide from mixed venous blood into the spirometer and uptake of other gases concentrating carbon dioxide in the spirometer. As P_{CO_2} reaches the level of $P\bar{v}_{CO_2}$, transfer of carbon dioxide from mixed venous blood into the spirometer ceases, but uptake of other gases continues. P_{CO_2} in the spirometer continues to increase to an equilibration point slightly above $P\bar{v}_{CO_2}$, where the tendency of carbon dioxide in the spirometer to increase because of uptake of other gases is balanced by uptake of carbon dioxide from the spirometer into blood.

Webb and Nunn [12] calculated the changes in volume of a lung unit to which the airway became occluded while its blood flow remained constant at 11 % of total pulmonary blood flow. They found that if $F_{I_{O_2}}$ 1.0 was breathed at the time of occlusion, complete collapse of the lung unit took 10 min. If a nitrous oxide–oxygen mixture with an $F_{I_{O_2}}$ of 0.3 was breathed before and after the occlusion, collapse took 7 min. These results are in general agreement with our experimental findings. Unfortunately the article does not provide enough information to enable reproduction of their calculations.

Imagine that we could measure the volume and composition of gas within the lung after right main bronchus occlusion. Compare this with the experimental preparation. There are several important differences. First, with bronchial occlusion the lung volume forms the "closed collapsible cavity". In the experimental preparation it is formed by the combination of the volume added to the spirometer (1000 ml), the deadspace in the spirometer (181 ml) and the gas in the lumen of the double-lumen tube, the tubing leading to the spirometer and the gas analysers (162 ml), and lung volume (750 ml; estimated 30 ml kg^{-1} for 25-kg dog). Thus the volume of this cavity is approximately three times the lung volume. Uptake of gas would thus take three times as long to reach completion. There is no change, however, in the ratio (rate of uptake with gas mixture A: rate of uptake with gas mixture B) at a given fraction of the time taken for gas uptake to reach completion [9]. Second, in the experimental preparation the spirometer was filled with inspired gas that diluted the alveolar gas. Third, in the experimental preparation gas uptake could be studied only until the spirometer had emptied. We estimated 950 ml BTPS to be roughly half the volume of the cavity formed by the spirometer, tubing and lung volume. T_{950} is only valid as an index of gas uptake, if gas uptake is relatively constant over this volume. When nitrogen is included in the inspired gas mixture, T_{950} is not a valid index of gas uptake, as there is an initial period of rapid gas uptake followed by a slower rate of uptake when constant composition is reached [8, 9]. Theoretical analysis [9] and analysis of the volume recordings from this experiment demonstrate that when breathing nitrous oxide–oxygen mixtures the rate of uptake is relatively constant, allowing T_{950} to be used as a reasonable index of the rate of gas uptake. To compare rates of uptake with various nitrous oxide–oxygen mixtures, Dale and Rahn [8] measured the rate of uptake during constant composition. This could not be done when studying nitrous oxide–oxygen mixtures, because a state of constant composition is often not reached. Fourth, in the experimental preparation, there are mechanical effects of the circuit and spirometer on the lung that might delay gas mixing or produce alterations in blood flow to the right lung. Fifth, in the experimental preparation the lung is rebreathing from a closed system with zero fresh gas flow, so there are normal rhythmic ventilatory movements. Finally, atelectasis does not occur in the experimental preparation. Therefore, it does not measure atelectasis directly, instead it studies the process of gas exchange believed to underlie the development of absorption atelectasis.

This study showed that when a nitrous oxide–oxygen mixture with $FI_{O_2} > 0.3$ is breathed, the rate of gas uptake from an unventilated lung is faster than with 100% oxygen. This implies that these gas mixtures accelerate absorption atelectasis. It is not certain that absorption atelectasis is a significant factor in the genesis of perioperative collapse, and only clinical studies may inform us if avoiding certain gas mixtures reduces perioperative atelectasis. This study showed also that when nitrous oxide–oxygen mixtures are breathed, P_{O_2} within an area of non-ventilated lung does not always rapidly equilibrate with $P\bar{v}_{O_2}$. Models of gas uptake from an area of unventilated lung should not assume instantaneous equilibration of P_{O_2} with mixed venous blood.

Acknowledgements

This work was funded in part by the Australian and New Zealand College of Anaesthetists. We wish to acknowledge the assistance of P. Herbison (Biostatistician, University of Otago Medical School) in the design and statistical analysis of this trial.

References

1. Goodman LR. Postoperative chest radiograph. 1. Alterations after abdominal surgery. *American Journal of Roentgenology* 1980; **134**: 533–541.
2. Benjamin JJ, Cascade PN, Rubenfire M, Wajszczuk W, Kerin NZ. Left lower lobe atelectasis and consolidation following cardiac surgery: The effect of topical cooling on the phrenic nerve. *Radiology* 1982; **142**: 11–14.
3. Rigg JRA. Pulmonary atelectasis after anaesthesia: Pathophysiology and management. *Canadian Anaesthetists' Society Journal* 1981; **28**: 305–313.
4. Burford GE. The use of inert gases in anesthesia atmospheres: Relationship to the problem of postoperative pulmonary complications. *Anesthesia and Analgesia* 1938; **17**: 241–251.
5. Dantzker DR, Wagner PD, West JB. Instability of lung units with low VA/Q ratios during O_2 breathing. *Journal of Applied Physiology* 1975; **38**: 886–895.
6. West JB, Wagner PD. Pulmonary gas exchange. In: West JB, ed. *Bioengineering Aspects of the Lung*. New York: Marcel Dekker Inc., 1977; 361–457.
7. Coryllos PN, Birnbaum GL. Studies in pulmonary gas absorption in bronchial obstruction. *American Journal of the Medical Sciences* 1932; **183**: 317–359.
8. Dale WA, Rahn H. Rate of gas absorption during atelectasis. *American Journal of Physiology* 1952; **170**: 606–615.
9. Joyce CJ, Baker AB, Kennedy RR. Gas uptake from an unventilated area of lung: computer model of absorption atelectasis. *Journal of Applied Physiology* 1993; **74**: 1107–1116.
10. Lichtheim L. Versuche über Lungenatelektase. *Archiv für Experimentellen Pathologie und Pharmakologie* 1879; **10**: 54–100.
11. Ernsting J. Rate of gas absorption from the lung during rebreathing in the dog. *Journal of Physiology (London)* 1965; **181**: 42P–43P.
12. Webb SJS, Nunn JF. A comparison between the effect of nitrous oxide and nitrogen on arterial P_{O_2}. *Anaesthesia* 1967; **22**: 69–81.
13. Don HF, Wahba M, Cuadrado L, Kelkar K. The effect of anesthesia and 100 per cent oxygen on the functional capacity of the lungs. *Anesthesiology* 1970; **32**: 521–529.
14. Don HF, Wahba WM, Craig DB. Airway closure, gas trapping, and the functional residual capacity during anesthesia. *Anesthesiology* 1972; **36**: 533–539.
15. Dueck R, Prutow RJ, Davies NJH, Clausen JL, Davidson TM. The lung volume at which shunting occurs with inhalation anesthesia. *Anesthesiology* 1988; **69**: 854–861.
16. Hedenstierna G. Gas exchange during anaesthesia. *Acta Anaesthesiologica Scandinavica* 1990; **34**: 27–31.
17. Hedenstierna G, Strandberg A, Brismar B, Lundquist H, Svensson L, Tokics L. Functional residual capacity, thoracoabdominal dimensions and central blood volume during general anesthesia with muscle paralysis and mechanical ventilation. *Anesthesiology* 1985; **62**: 247–254.
18. Hewlett AM, Hulands GH, Nunn JH, Heath JR. Functional residual capacity during anaesthesia. II. Spontaneous respiration. *British Journal of Anaesthesia* 1974; **46**: 486–494.
19. Hewlett AM, Hulands GH, Nunn JH, Milledge JR. Functional residual capacity during anaesthesia. III. Artificial ventilation. *British Journal of Anaesthesia* 1974; **46**: 495–503.
20. Krayer S, Rehder K, Beck KC, Cameron PD, Didier EP, Hoffman EA. Quantification of thoracic volumes by three-dimensional imaging. *Journal of Applied Physiology* 1987; **62**: 591–598.
21. Rehder K, Marsh HM. Respiratory mechanics during anaesthesia and mechanical ventilation. In: Farhi LE, Tenney SM, eds. *Handbook of Physiology. Section 3. The Respiratory System, vol. 3. Mechanics of Breathing Part 2*. Bethesda, MD: American Physiological Society, 1986; 737–752.
22. Wahba RWM. Perioperative functional residual capacity. *Canadian Journal of Anaesthesia* 1991; **38**: 384–400.
23. Bergman NA, Tien YK. Contribution of the closure of pulmonary units to impaired oxygenation during anesthesia. *Anesthesiology* 1983; **59**: 395–401.
24. Weenig CS, Pietak S, Hickey RF, Fairley HB. Relationship of preoperative closing volume to function residual capacity and alveolar–arterial oxygen difference during anesthesia with controlled ventilation. *Anesthesiology* 1974; **41**: 3–7.
25. Hochberg Y, Tamhane AC. *Multiple Comparison Procedures*, 1st Edn. New York: John Wiley and Sons, 1987.
26. Milliken GA, Johnson DE. *Analysis of Messy Data, vol. 1: Designed Experiments*, 1st Edn. London: Lifetime Learning Publications, 1984.
27. Loring SH, Butler JP. Gas exchange in body cavities. In: Farhi LE, Tenney SM, eds. *Handbook of Physiology. Section 3. The Respiratory System*, vol. 4, *Gas Exchange*. Bethesda, MD: American Physiological Society, 1987; 283–295.
28. Nunn JF, Williams IP, Jones JG, Hewlett AM, Hulands GH, Minty BD. Detection and reversal of pulmonary absorption collapse. *British Journal of Anaesthesia* 1978; **50**: 91–99.
29. Piiper J, Canfield RE, Rahn H. Absorption of various inert gases from subcutaneous gas pockets in rats. *Journal of Applied Physiology* 1962; **17**: 268–274.
30. Tenney SM, Carpenter FG, Rahn H. Gas transfer in a sulfur hexafluoride pneumoperitoneum. *Journal of Applied Physiology* 1953; **6**: 201–208.
31. Tucker RW, Tenney SM. Inert gas exchange in subcutaneous gas pockets of air breathing animals: Theory and measurement. *Respiration Physiology* 1966; **1**: 151–171.

British Journal of Anaesthesia 1996; **76**: 297–299

Interpleural local anaesthesia: anatomical basis for mechanism of action

A. G. McKenzie and S. Mathe

Summary

India ink was injected through an extradural catheter placed in the right interpleural space in cadavers at autopsy. The lung was removed and the spread of the ink noted and photographed. In six cadavers, block sections were cut at the anterior axillary line through three ribs, intercostal muscles and parietal pleura. The blocks were fixed in formalin and then decalcified, sectioned, stained and mounted on slides. In all cases the ink covered the chest wall, lung and diaphragm, and was seen to pool in the paravertebral area. Examination of the histological slides revealed black pigment on the pleural surface and in the subpleural space. The mechanism of transport across the parietal pleura is discussed. (*Br. J. Anaesth.* 1996; **76**: 297–299)

Key words
Anaesthetic techniques, regional, interpleural.

Since the introduction of interpleural local analgesia in 1984 by Kvalheim and Reiestad [1], there have been numerous reports on the use and complications of the technique in the management of different types of pain [2]. However, there have been few investigations into the mechanism of action, which remains conjectural.

In the original abstract [1], Kvalheim and Reiestad suggested a mechanism of reverse diffusion of local anaesthetic through the parietal pleura into the subpleural space. From there, as shown in 1980 by Nunn and Slavin [3], the fluid could pass between the flimsy fascicles of the intercostalis intimus muscle to the intercostal space(s) and nerve(s). This mechanism seems to be supported by the observation of Miserocchi and colleagues [4], using gamma camera imaging, that a major distribution of fluid injected into the pleural cavity of anaesthetized dogs is in the paravertebral area, where the intercostal nerves are covered only by parietal pleura. Further support has come from studies on interpleural local anaesthetic in dogs, using somatosensory evoked potentials [5], and in patients using computed tomography [6].

The aim of this study was to investigate the spread of fluid injected into the pleural space of cadavers and, in particular, to determine if transport occurs through the parietal pleura.

Materials and methods

The study received ethics approval from the Medical Research Council of Zimbabwe. Criteria for the cadavers were that they were adult, scheduled for autopsy and without chest trauma or deformity. All cadavers had been refrigerated promptly and autopsy was performed within 48 h after death. Each cadaver was placed in the left lateral position and an extradural catheter inserted interpleurally through the right eighth intercostal space at the posterior axillary line. The interpleural space was located by the loss of resistance technique using a Tuohy needle and saline-filled syringe. The catheter was advanced 5–6 cm into the space between the parietal and visceral pleura, and the needle withdrawn. After successfully siting the catheter it was taped in position and the cadaver turned to the supine position. Then 20 ml of India ink was injected through the interpleural catheter and the cadaver left undisturbed for 30 min.

Following this, the chest was opened and the right lung removed carefully. The spread of ink within the thorax was noted and photographed. At the anterior axillary line, block sections were cut carefully through three ribs, intercostal muscles and parietal pleura. The specimens were fixed in 10% formalin before further histological preparation, which was performed in the following steps: (i) decalcification in formic acid–citric acid solution; (ii) routine processing and embedding in paraffin wax; (iii) cutting of 5 µm thick sections and staining with haematoxylin and eosin; and (iv) mounting on slides.

Results

No difficulties occurred during insertion of the interpleural catheters; interpleural injection of India ink was performed on seven cadavers. In one case, an empyema was found on opening the chest and this subject was withdrawn from the study (although the

---

A. G. McKenzie*, BPHARM, MB, CHB, FRCA, Division of Anaesthetics, Parirenyatwa Hospital, Harare, Zimbabwe. S. Mathe, MB, CHB, MRCPATH, Department of Pathology, Mpilo Central Hospital, Bulawayo, Zimbabwe. Accepted for publication: October 2, 1995.

*Present address for correspondence: Department of Anaesthesia, Eastern General Hospital, Seafield Street, Edinburgh EH6 7LN.

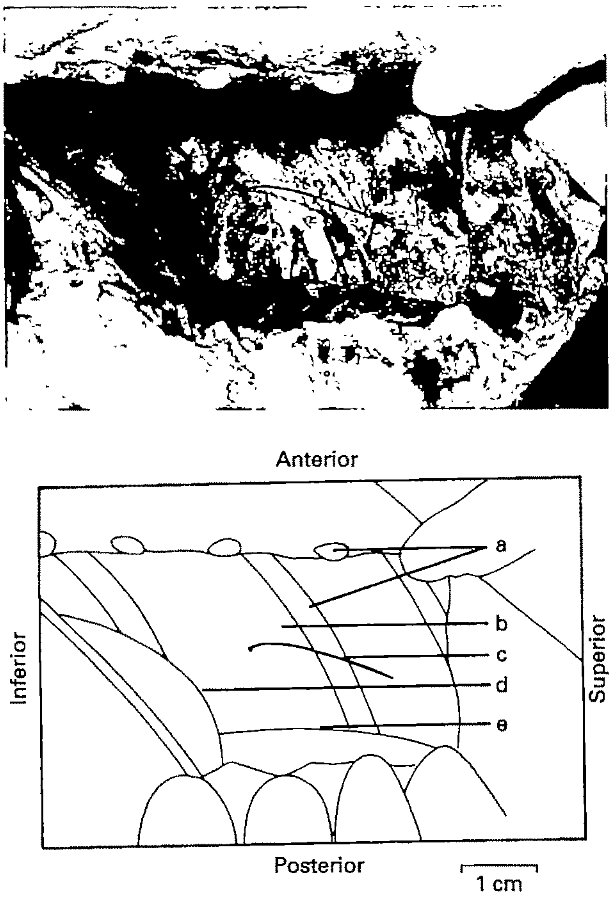


Figure 1 Top: distribution of India ink in the right hemithorax, 30 min after interpleural injection. The lung has been removed. The interpleural catheter is in the centre of the photograph. Bottom: line drawing for identification of structures above: a = rib, b = parietal pleura, c = catheter, d = diaphragm, e = paravertebral pooling of India ink.

spread of ink appeared to be wide). In each of the remaining six cases it was found that the catheter was well located in the interpleural space and the spread of ink was uniformly wide. The ink almost completely covered the chest wall, lung and diaphragm, tending to pool in the paravertebral area (fig. 1).

Examination of the histological slides prepared from all six specimens revealed normal bone, skeletal muscle and nerve tissue with black pigment on the pleural surface and in the subpleural space (figs 2, 3).

Discussion

Several studies have used cadavers injected with India ink to simulate intercostal nerve block [3, 7, 8]. Although the clinical relevance of India ink has been questioned [9], the differences between spread of India ink and local anaesthetic–indicator solution appear to have been quantitative rather than qualitative, as have differences between cadavers and patients. India ink is the most suitable dye when histological slides are required. It comprises a dispersion of carbon black in water; the suspension is stabilized with various agents. Carbon black is an extremely finely divided form of amorphous carbon. The particle size of the commercial grade used for India ink is 13–75 nm (0.013–0.075 μm) [10].

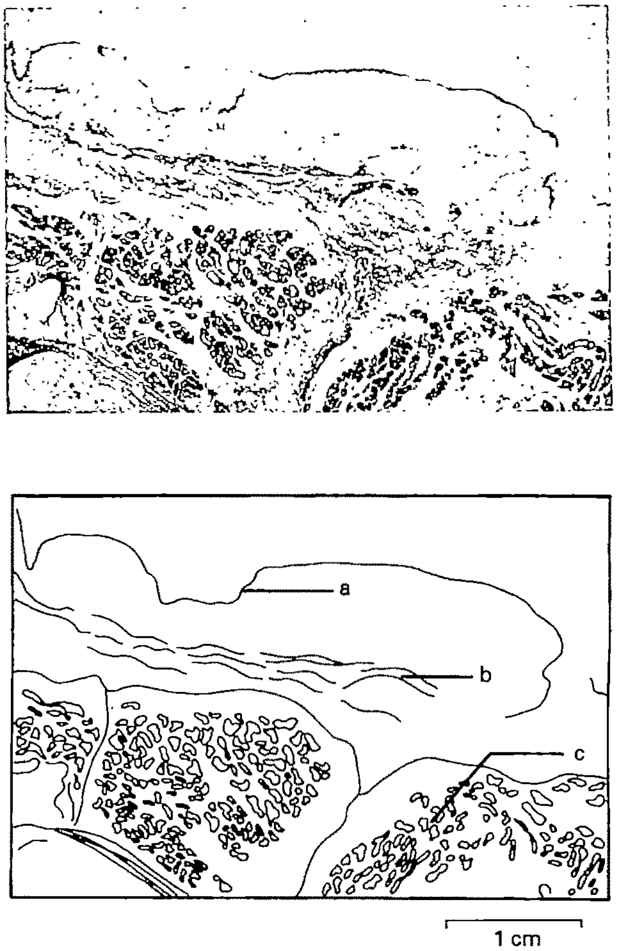


Figure 2 Top: photomicrograph of transverse section through the rib, intercostal muscle and parietal pleura after interpleural injection of India ink. Black pigment is visible on the pleural surface (×2.5 objective). Bottom: schematic diagram explaining the above: a = parietal pleura with black pigment on surface, b = black pigment in subpleural space, c = muscle cells.

The subpleural black pigment revealed in the histological slides was *not* regarded as formalin artefact, because it did not appear in bone in any of the slides. The pigment was also *not* considered to be melanin, because the subpleural tissue is too deep. We conclude that our results demonstrated movement of interpleural India ink (in cadavers) through the parietal pleura to the subpleural space.

Both parietal and visceral pleural surfaces are lubricated by a thin film of tissue fluid. Liquid injected into the pleural space is therefore added to tissue fluid. Two important differences have been observed between the parietal and visceral pleura [11]: (1) parietal pleura has stomata between the mesothelial cells (which form a single layer lining). These stomata are 2–12 μm in diameter; (2) the fibroelastic layer of the parietal pleura is much thinner, suggestive of a membrane compatible with fluid transport.

Diffusion in liquids is a slow process yet the onset of interpleural local anaesthesia is reported to be about 15 min. This suggests that the mechanism of transport across the parietal pleura may be more than diffusion, perhaps bulk flow. Transfer by macrophage activity may occur, but is excluded in this particular study, as cadavers were used.

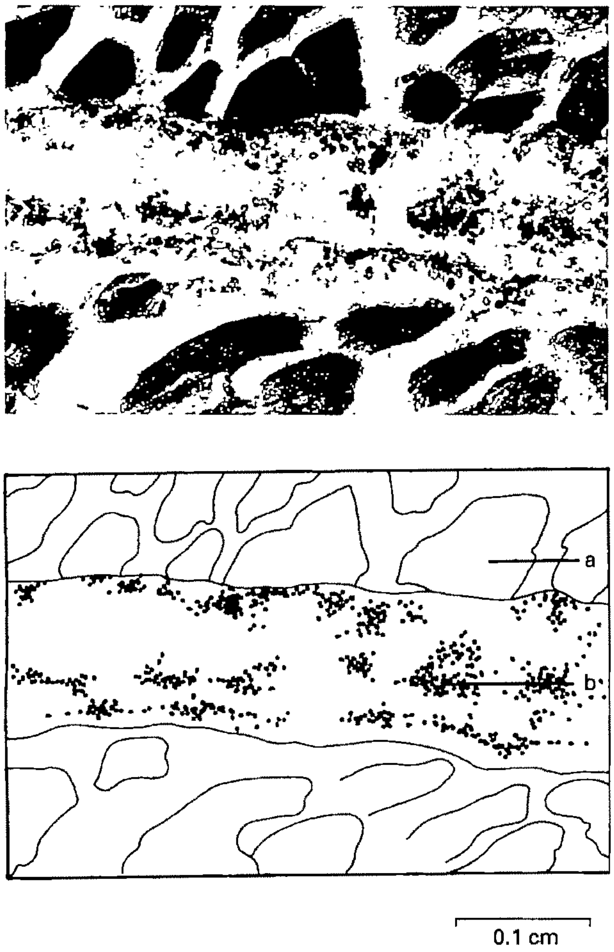


Figure 3 Top: photomicrograph of similar transverse section showing black pigment between muscle fibres (×25 objective). Bottom: schematic diagram explaining the above: a = muscle fibres (cut transversely), b = black pigment between muscle fibres.

Acknowledgements

We thank the Medical Research Council of Zimbabwe for permission to carry out this study and publish the findings. We also thank Dr J. H. McClure, Department of Anaesthetics, Royal Infirmary of Edinburgh, for helpful advice on the preparation of the manuscript.

References

1. Kvalheim L, Reiestad F. Interpleural catheter in the management of postoperative pain. *Anesthesiology* 1984; **61**: A231.
2. Murphy DF. Interpleural analgesia. *British Journal of Anaesthesia* 1993; **71**: 426–434.
3. Nunn JF, Slavin G. Posterior intercostal nerve block for pain relief after cholecystectomy. Anatomical basis and efficacy. *British Journal of Anaesthesia* 1980; **52**: 253–259.
4. Miserocchi G, Pistolesi M, Miniati M, Bellina CR, Negrini D, Giuntini C. Pleural liquid pressure gradients and intrapleural distribution of injected bolus. *Journal of Applied Physiology* 1984; **56**: 526–532.
5. Riegler FX, VadeBoncouer TR, Pelligrino DA. Interpleural anesthetics in the dog: Differential somatic neural blockade. *Anesthesiology* 1989; **71**: 744–750.
6. Stromskag KE, Hauge O, Steen PA. Distribution of local anaesthetics injected into the interpleural space, studied by computerized tomography. *Acta Anaesthesiologica Scandinavica* 1990; **34**: 323–326.
7. Moore DC. Intercostal nerve block: spread of India ink injected to the rib's costal groove. *British Journal of Anaesthesia* 1981; **53**: 325–329.
8. Murphy DF. Continuous intercostal nerve blockade. An anatomical study to elucidate its mode of action. *British Journal of Anaesthesia* 1984; **56**: 627–629.
9. Mowbray A, Wong KKS. Low volume intercostal injection. A comparative study in patients and cadavers. *Anaesthesia* 1988; **43**: 633–634.
10. Dannenberg EM. Carbon black. In: *Encyclopedia of Chemical Technology*, *vol. 4*, 3rd Edn. New York: Interscience, 1978; 643.
11. Carter D, True L, Otis CN. Serous membranes. In: Sternberg SS, ed. *Histology for Pathologists*. New York: Raven Press, 1992; 500–501.

British Journal of Anaesthesia 1996; **76**: 300–307

REVIEW ARTICLE

Ropivacaine

J. H. McClure

Ropivacaine is a new aminoamide local anaesthetic. It is the monohydrate of the hydrochloride salt of 1-propyl-2′,6′-pipecoloxylidide and is prepared as the pure *S*-enantiomer. It is one of a group of local anaesthetic drugs, the pipecoloxylidides (fig. 1), which were first synthesized in 1957 [3]. Mepivacaine and bupivacaine are both well known members of this group and have been in clinical use for more than 30 years [4, 23, 82]. Mepivacaine has a methyl group, ropivacaine a propyl group and bupivacaine a butyl group on the piperidine nitrogen atom of the molecule.

The pipecoloxylidides are chiral drugs because the molecules possess an asymmetric carbon atom (fig. 1) and they may have a left-(sinister) or right-(rectus) handed configuration. Mepivacaine and bupivacaine are currently produced for clinical use as racemic mixtures of the enantiomers containing equal proportions of the "*S*" and "*R*" forms but ropivacaine is the single "*S*" enantiomer. It has an enantiomeric purity of 99.5 % and is prepared by the alkylation of the *S*-enantiomer of dibenzoyl-L-tartaric acid [25].

Differences in three-dimensional structure confer differences in the activity of enantiomers in the complex biological environment of the receptor [15]. This property of the pipecoloxylidides was known in the late 1960s because the different enantiomers had different durations of action at the target receptor in neural tissue [1, 47]. These differences in biological activity, whether measured in terms of desired or adverse effects, are not surprising because individual enantiomers bind to receptors or enzymes which are chiral amino acids with stereoselective properties. There may be differences in the activity of enantiomers of a drug: one may be active, the other partially active or inactive, or at the extreme, one may have an opposite effect to the other.

The clear advantages [22, 65, 72, 79, 80] of the long duration of action and sensory–motor differential block seen with bupivacaine consigned other members of this group of local anaesthetic drugs to the laboratory shelf, although some research work [2, 5] was carried out on the racemic mixture of the propyl homologue.

Historical background

In 1979, Albright published an alarming editorial [7] which associated the long-acting local anaesthetics, bupivacaine and etidocaine with cardiac arrest during regional anaesthesia. Albright reported six cases of presumed accidental intravascular injection of either bupivacaine or etidocaine which caused sudden ventricular arrhythmia occurring at the same time as severe convulsions. There were three cases of attempted brachial plexus block with 0.5 % bupivacaine, one i.v. regional anaesthetic with 0.5 % bupivacaine and chloroprocaine, one caudal extradural anaesthetic with etidocaine and, interestingly, only one case in this initial report was caused by 0.75 % bupivacaine used extradurally for Caesarean section. It was clear that there was a problem and there was a *paucity of experimental or clinical data delineating the effects of bupivacaine (and etidocaine) on the cardiovascular system above the convulsive threshold* at that time. Subsequently, sporadic cases of maternal death resulting from accidental i.v. injection of 0.75 % bupivacaine at the time of

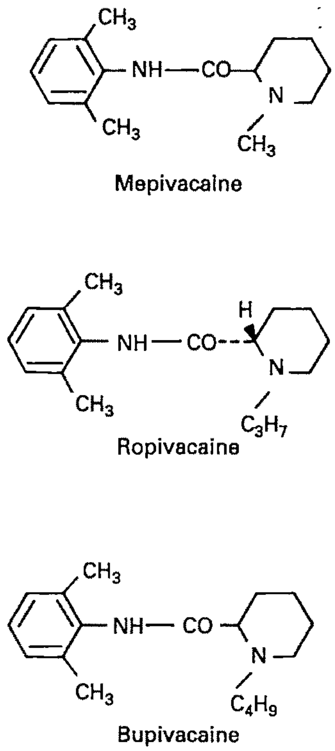


Figure 1 The pipecoloxylidides group of local anaesthetic drugs. The position of the asymmetric carbon atom is illustrated for ropivacaine.

(*Br. J. Anaesth.* 1996; **76**: 300–307)

Key words
Anaesthetic local, ropivacaine.

John H. McClure, bsc (hons), mb, chb, frca, Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW.

extradural anaesthesia for Caesarean section were reported [48]. In the UK there were five deaths after i.v. regional anaesthesia performed by trainee casualty officers. Malfunction of an automatic tourniquet and the drug, bupivacaine, were common factors in these deaths [31]. Albright subsequently presented his findings to the United States Food and Drug Administration (FDA) which issued urgent recommendations about bupivacaine which contained the specific statement that 0.75 % bupivacaine was no longer recommended for obstetric anaesthesia. This sequence of events provided the impetus to develop a new local anaesthetic drug. It was possible that a drug of a lower lipid solubility compared with bupivacaine was less cardiotoxic.

The high lipid solubility of bupivacaine confers benefit by reducing absorption from the intended site of action, for example the extradural space. However, this property is not relevant if this site is bypassed when the drug is injected directly into the circulation. When a large dose of bupivacaine is injected rapidly into a vein, it is transported to the heart and brain and there is a high concentration of free drug available to cross the lipoprotein membrane of conducting tissue by first-pass extraction [74, 75]. After accidental i.v. injection, the mass of plasma protein (α_1-acid glycoprotein and albumin) in the volume of blood exposed to the drug is quickly saturated leaving a significant mass of unbound drug available for diffusion into conducting tissue of the heart and brain.

The FDA recommendations, while initially seeming illogical, in that it was the drug and not the concentration that was potentially cardiotoxic, achieved their objective. Appropriate measures, including slow or fractionated administration of a high dose of local anaesthetic drug, to detect potential systemic toxicity, have reduced the risk significantly.

Physiochemical properties

The physiochemical properties of lignocaine, ropivacaine and bupivacaine are summarized in table 1. The relative lipid solubility of ropivacaine, as measured by partitioning studies between N heptane and buffer and relative mean uptake into rat sciatic nerves, shows ropivacaine to be intermediate between lignocaine and bupivacaine. Plasma protein binding of ropivacaine is marginally less than that of bupivacaine but the pK_a is identical.

Preclinical studies

PRIMARY PHARMACODYNAMICS

Rosenberg and Heinonen in 1983 [63], using isolated sheathed vagus and phrenic nerves of rats, showed that ropivacaine at low concentration (25–50 µmol litre^{-1}) produced a profound and rapid block of both Aδ and C fibres and was more potent than similar low concentrations of bupivacaine in blocking these fibres. At higher concentrations, ropivacaine and bupivacaine had similar blocking activity. A study comparing higher doses of drug on isolated sheathed rabbit vagus nerve [11] found that A fibre block was 16 % greater with bupivacaine than similar concentrations (100, 150 and 200 µmol litre^{-1}) of ropivacaine. The degree of C fibre block was similar with both drugs at these concentrations.

Wildsmith and colleagues [83], using desheathed rabbit vagus nerves, found that ropivacaine blocked C fibres faster than A fibres and was a potent producer of frequency- (or use-) dependent block, that is block which only occurs when the fibre is stimulated. Low pK_a and high lipid solubility of a local anaesthetic drug favoured A over C fibre block whereas the reverse was true for high pK_a and low lipid solubility. Frequency-dependent block is considered to be related to lipid solubility and the molecular weight of the local anaesthetic drug. The lower lipid solubility of ropivacaine compared with bupivacaine is presumed to retard penetration of myelin sheaths.

This greater degree of differential block with ropivacaine at low concentration and the property of producing frequency-dependent block were considered to offer considerable clinical advantages in providing analgesia with minimal motor block.

Infiltration anaesthesia

Subcutaneous administration of ropivacaine 1 ml (0.25–0.5 %) has been shown to reduce cutaneous blood flow in pigs, as assessed by the laser Doppler method [43]. Bupivacaine in similar concentrations increased cutaneous blood flow. The addition of adrenaline 5 µg ml^{-1} to both ropivacaine and bupivacaine solutions reduced blood flow. Ropivacaine (0.25 ml of 0.25–0.75 %) has been shown to be two to three times longer acting than similar doses of bupivacaine when administered intradermally in the guinea pig [5]. The duration of effect of both drugs was increased further by the addition of adrenaline

Table 1 Physical properties of lignocaine, ropivacaine and bupivacaine. Data derived from Rosenberg, Kytta and Alila [64]

	Lignocaine	Ropivacaine	Bupivacaine
Molecular weight (base)	234	274	288
pK_a	7.7	8.1	8.1
Partition coefficient (N heptane/buffer)	1	2.9	10
Mean uptake ratio (rat sciatic nerve)	1	1.8	3.3
Protein binding	65	94	95

5 μg ml^{-1}. An *in vitro* study on ring segments of the femoral artery and vein of dogs [54] confirmed that ropivacaine has a vasoconstrictive effect but this effect may be minimal with the doses used in clinical practice. No difference was found in skin blood flow or surgical bleeding when comparing 0.25% ropivacaine and bupivacaine given s.c. before skin incision in pigs [30]. However, the addition of adrenaline 5 μg ml^{-1} decreased blood flow by 50% when added to each drug.

Peripheral nerve block

Animal studies have shown that 0.5–1% ropivacaine consistently produces effective sensory and motor anaesthesia in sciatic nerve and brachial plexus block. Neither increasing the concentration above 0.75% nor adding adrenaline were found to significantly improve the duration of motor or sensory anaesthesia in peripheral nerve block. Onset time and duration of block were shorter with ropivacaine than equal concentrations of bupivacaine in the rat [28].

Central blocks

In extradural and spinal anaesthesia in the guinea pig, mouse and dog, ropivacaine and bupivacaine were found to be equipotent in terms of sensory block but the duration of motor block was shorter with ropivacaine [5, 28].

SECONDARY PHARMACODYNAMICS

In vivo *studies*

The toxic effects of local anaesthetics on the brain and heart provided the initial stimulus to develop ropivacaine and much of the early animal research involved assessment of the potential of this new drug to cause cardiotoxicity. Central nervous system (CNS) toxicity is related directly to the anaesthetic potency of local anaesthetic drugs and similar doses of ropivacaine and bupivacaine have been found to cause convulsions in conscious dogs [26, 27]. Early work showed little difference between the cardiotoxic effect of a bolus dose of ropivacaine or bupivacaine in sheep [66, 67] but at supraconvulsant doses in dogs [26] ropivacaine was less arrhythmogenic than bupivacaine. This reduced cardiotoxic potential with ropivacaine was confirmed subsequently in sheep and the ratio of fatal doses was 1:2:9 for bupivacaine:ropivacaine:lignocaine [55].

The effect of local anaesthetic on the electrophysiology of the heart has been defined further. The maximal rate of increase in the cardiac action potential (*V*max) is largely dependent on sodium ion influx via the sodium channels. All local anaesthetic drugs are known to depress *V*max in a dose-dependent manner depending on the membrane potential and rate of stimulation. Bupivacaine depresses *V*max considerably more than lignocaine and results in slowed conduction of the cardiac action potential which is manifest by prolongation of the PR and QRS intervals of the electrocardiograph [62]. This results in re-entrant phenomena and ventricular arrhythmia [37]. When bupivacaine is bound to cardiac muscle, recovery from block is slow. The sodium channels are blocked in a "fast-in, slow-out" manner which causes difficulty in resuscitation when ventricular fibrillation has occurred. Studies suggest that the cardiotoxicity of bupivacaine results from its high lipid solubility and that the "*R*" enantiomer is more toxic than the "*S*" enantiomer [77].

Ropivacaine is intermediate in its depressant effect on *V*max in guinea pig papillary muscle between bupivacaine (highest) and lignocaine (lowest) and recovery from block is slower with bupivacaine [8]. Moller and Covino, in two studies [50, 51], confirmed that ropivacaine was intermediate between bupivacaine and lignocaine in decreasing *V*max in isolated rabbit Purkinje fibres. Exogenous progesterone had no additional effect on depression of *V*max with ropivacaine in contrast with the effect of bupivacaine where depression of *V*max was increased [51]. This was considered to reflect the increased susceptibility to cardiotoxicity with bupivacaine seen in pregnancy.

A favourable cardiotoxic profile of ropivacaine compared with bupivacaine was confirmed in pigs [61]. An electrophysiological toxicity ratio, based on the inverse of the amount of local anaesthetic agent required to prolong the QRS interval to the same degree, was determined as 1:6.7:15 for lignocaine, ropivacaine and bupivacaine.

The cardiotoxicity of ropivacaine is not enhanced by pregnancy in sheep [68]. Early work [52] found that pregnancy enhanced the cardiotoxic effects of bupivacaine, but this has since been refuted [69]. Greater doses of ropivacaine (12.9 ± 0.8 mg kg^{-1}) compared with bupivacaine (8.5 ± 1.2 mg kg^{-1}) are required to produce circulatory collapse in pregnant ewes. Pregnancy did not appear to alter plasma protein binding by both drugs.

Bupivacaine has also been found to be more cardiotoxic than equivalent doses of lignocaine or ropivacaine in the isolated perfused rabbit heart (Langendorff preparation) [60]. Bupivacaine produced more severe arrhythmias than those observed with ropivacaine; lignocaine was devoid of arrhythmogenicity. The development of ECG disturbances and severe myocardial depression was more rapid with bupivacaine than ropivacaine.

Ropivacaine administered by i.v. infusion was found to be less toxic than bupivacaine in human volunteers. Mild CNS symptoms and minor cardiovascular toxicity, as measured by changes in conductivity and contractability, occurred at lower dosage and lower plasma concentration with bupivacaine compared with ropivacaine [70].

PHARMACOKINETICS

The pharmacokinetics of ropivacaine and bupivacaine after i.v. and extradural administration have been determined in the dog and Rhesus monkey [9, 40]. The effect of adrenaline on extradural administration has also been evaluated. The concentration of ropivacaine decreases more rapidly than bupivacaine during the elimination phase after i.v. infusion. Mean clearance (*Cl*) for ropivacaine in the dog was 41.1 ± 8.2 ml min^{-1} kg^{-1} compared with 32.3 ± 4.8 ml min^{-1} kg^{-1} for bupivacaine, although this difference was not statistically significant. After extradural administration the pharmacokinetic profiles of the two drugs were similar. Peak arterial ropivacaine concentration ($C_P$max) after extradural injection was higher for ropivacaine than bupivacaine with the 0.25 % concentration. The addition of adrenaline to either drug administered extradurally did not decrease $C_P$max consistently. The pharmacokinetic profiles of ropivacaine and bupivacaine in humans after extradural administration are similar to those determined in animal studies [38, 78].

The pharmacokinetic characteristics of ropivacaine after i.v. infusion have been determined in human volunteers [46]. Clearance (0.82 ± 0.16 litre min^{-1}) was found to be higher than the previously determined value for bupivacaine (0.58 litre min^{-1}). Plasma binding of ropivacaine averaged 94 ± 1 % (slightly lower than bupivacaine) and volume of distribution at steady state (V^{ss}) based on blood drug concentration was 59 ± 7 litre (cf. bupivacaine 73 litre). The terminal elimination half-life was 111 ± 62 min which is less than that determined previously for bupivacaine [75]. The higher clearance of ropivacaine compared with bupivacaine may offer an advantage in terms of systemic toxicity.

Human volunteer and clinical studies

The potency of ropivacaine in terms of sensory and motor block has now been determined in clinical use. A large number of open and double-blind studies have been performed on human volunteers and patients to determine the efficacy and degree of differential block with ropivacaine compared with bupivacaine in peripheral and central neural block.

Infiltration anaesthesia

Studies have been performed in human volunteers to determine the effect of ropivacaine compared with bupivacaine on cutaneous blood flow after intradermal injection of 0.1 ml of drug. Both bupivacaine and lignocaine produce vasodilatation in human skin, but a low concentration (0.25 %) of ropivacaine decreases skin blood flow [18]. Adrenaline 5 µg ml^{-1} reduces flow maximally when used alone but ropivacaine diminishes and does not accentuate the vasoconstrictive effect of adrenaline [19]. Plain solutions of ropivacaine produce a significantly longer duration of dermal analgesia than plain solutions of bupivacaine. Adrenaline significantly increases duration with both drugs [16]. The intradermal administration of small doses of local anaesthetic drug provides an interesting experimental model but this cutaneous vasoconstriction is observed with low doses and is not considered to be clinically important.

Ropivacaine (70 ml of 0.25 %) infiltrated into cholecystectomy wounds significantly decreases wound pain and increases the time to the first request for postoperative analgesia compared with saline [36]. However, wound infiltration with 0.25 % ropivacaine or bupivacaine 40 ml was equally effective in the management of post-herniorrhaphy pain [24]. There was no clinically significant difference between ropivacaine and bupivacaine in terms of duration of block or intensity of pain relief.

Peripheral nerve block

In a dose–response study in human volunteers undergoing bilateral ulnar nerve block, it was found that ropivacaine 2 ml was maximally effective at concentrations between 0.5 % and 0.75 % [58]. The profile of action resembled bupivacaine. The addition of adrenaline had no effect on onset time or duration of action of ropivacaine or bupivacaine. Several cases of residual paraesthesia lasting for longer than 1 month were observed with ropivacaine and bupivacaine. This was considered to result from needle trauma as there was no difference between ropivacaine and bupivacaine and there was no correlation with dose [58].

In a pharmacokinetic study bilateral intercostal block (T5–11) was performed in volunteers [44] using a total of 0.25 % plain ropivacaine or bupivacaine 56 ml. There was no difference in maximum plasma concentration ($C_P$max) but this tended to peak (tC_Pmax) earlier with ropivacaine. The terminal half-life $T_{\frac{1}{2}}^{\beta}$) was significantly shorter with ropivacaine. Sensory and motor block were of shorter duration with ropivacaine (6.0 ± 2.5 h) compared with bupivacaine (10.0 ± 3.0 h).

Brachial plexus block

Hickey and colleagues [32–35] studied ropivacaine in subclavian perivascular brachial plexus block. The addition of adrenaline to 0.5 % ropivacaine was not found to alter the pharmacokinetic properties of ropivacaine absorbed from the brachial plexus sheath. Ropivacaine 0.5 % was comparable with 0.5 % bupivacaine in terms of onset time and duration of effect, and motor block was profound with both drugs.

Lumbar extradural block

Open studies [20, 57, 81] of lumbar extradural administration of ropivacaine in concentrations of 0.5 %, 0.75 % and 1 % showed that ropivacaine was a long-acting local anaesthetic which gave surgical anaesthesia of good quality. Increasing the concentration decreased onset time and increased motor block, as occurs with other local anaesthetic agents [71]. The peak plasma concentration ($C_P$max) of ropivacaine was below the concentration associated with systemic toxicity in animals. Comparison of 0.5 % bupivacaine and ropivacaine showed that bupivacaine had a slightly longer duration of sensory and motor block but spread was similar [14]. Katz, Knarr and Bridenbaugh [39] compared 0.75 % ropivacaine 20 ml with 0.5 % bupivacaine 20 ml and no major differences were noted except that the time to two dermatome segment regression was of longer duration with 0.75% ropivacaine compared with 0.5% bupivacaine. Two studies [56, 85] comparing 1% ropivacaine and 0.75% bupivacaine found no difference in terms of onset, extent or duration of motor block but the duration of sensory block was longer and clinical efficacy was better with 1% ropivacaine compared with 0.75% bupivacaine. In elective hip surgery, 1% ropivacaine provided satisfactory anaesthesia more frequently than 0.5% bupivacaine and the duration of sensory and motor block was significantly longer [84]. The addition of adrenaline 5 μg ml^{-1} to 0.5% and 0.75% ropivacaine or bupivacaine did not appear to confer any advantage in terms of duration of action [17]. There were also no differences in block or cardiovascular effect other than those expected from extradural block itself [41, 42].

Brockway and colleagues [12] compared 0.5%, 0.75% and 1% ropivacaine 15 ml with 0.5% and 0.75% bupivacaine 15 ml in 110 patients and found no significant difference in onset, spread or duration of sensory block when similar concentrations were compared. However, ropivacaine produced a slower onset, shorter duration and less intense motor block than the same concentration of bupivacaine. Interestingly, four patients in this study, who were excluded from analysis of extradural block, received accidental i.v. injections which were not detected with a test dose of 1% lignocaine with adrenaline 3 ml. No patient, including one patient who received a total dose of 112.5 mg of ropivacaine, suffered from harmful systemic toxicity as a slow incremental injection of the main dose was given.

In a study of clinical efficacy and kinetics of the lumbar extradural administration of 10 ml of 1%, 20 ml of 0.5% ropivacaine and 20 ml of 0.5% bupivacaine, Morrison and colleagues [53] observed no difference between the groups in terms of onset, duration and spread of sensory block. Motor block produced by 0.5% ropivacaine was less intense and of shorter duration than that of 0.5% bupivacaine. The $C_P$max of ropivacaine was significantly greater and the terminal phase $T_{\frac{1}{2}}$ significantly shorter than that of bupivacaine.

Two volunteer studies of lumbar extradural block are considered pivotal in the interpretation of clinical data as they are the only studies which measured motor block in a quantitative manner. The modified Bromage scale [13] is simple to apply in a clinical setting and analyses movement in various muscle groups. It is a qualitative measure of spread and intensity of block. Mechanical measurement of the isometric muscle force (IMF) in a single muscle group is a more valid measurement of intensity of motor block [10, 45, 59, 87], although it is difficult to apply in the clinical situation and hence the importance of these volunteer studies.

In the first study [86] 0.5%, 0.75% or 1% ropivacaine 20 ml was given to 30 volunteers (10 in each group) in a bolus dose. Motor block was assessed by quantitative (IMF in separate muscle groups) and qualitative (modified Bromage scale) methods. Onset of motor block, as assessed by the quantitative method, was significantly slower with 0.5% ropivacaine and the intensity and duration of motor block increased with increasing dose. Motor block measured by the modified Bromage scale showed only the first part of the regression phase. Full recovery of muscle strength, as assessed by the qualitative method (Bromage scale = 0), was attained 1.5 to 2.5 h earlier than that assessed by the quantitative method.

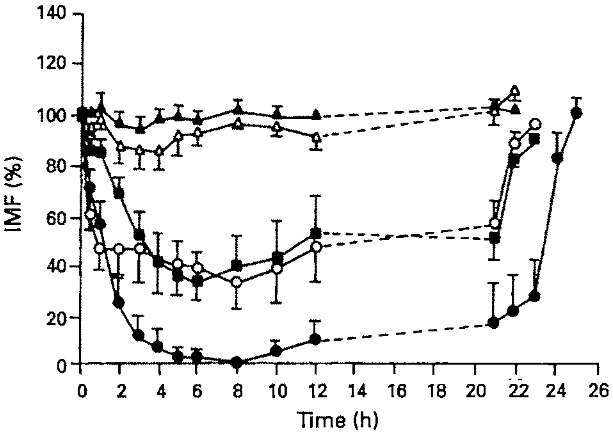


Figure 2 Motor block of the muscles of knee flexion in the 0.1% (△), 0.2% (■) and 0.3% (○) ropivacaine groups, and in the 0.25% bupivacaine (●) and saline (▲) groups (mean, SEM). IMF = Isometric muscle force. Reprinted with permission from Zaric and colleagues [88].

In the second study [88], volunteers (eight in each group) received a bolus dose of 0.1%, 0.2% or 0.3% ropivacaine 10 ml or 0.25% bupivacaine 10 ml followed by a continuous infusion of 10 ml h^{-1} of the same drug and concentration for 21 h. Similar sensory spread was seen in all groups. Bupivacaine 0.25% caused motor block of the greatest intensity as assessed quantitatively by IMF in three separate muscle groups. The regression phase of motor block when the infusion was stopped at 21 h was significantly shorter with all three concentrations of ropivacaine than with bupivacaine. This was seen most clearly in the knee flexors (fig. 2) but a similar profile was seen in the abdominal muscles and plantar flexors of the foot. This similar spread of sensory block, the reduced intensity of motor block and quick recovery observed with infusions of 0.2% and 0.3% ropivacaine compared with 0.25% bupivacaine offer distinct advantages in the clinical setting during extradural analgesia for labour or postoperative pain.

Spinal block

In a safety study, subarachnoid administration of 0.5% or 0.75% glucose free (plain) ropivacaine 3 ml were compared [76]. The incidence of complete motor block, as assessed by a qualitative method, was higher with 0.75% (18 of 20) compared with 0.5% (10 of 19) ropivacaine. The duration of analgesia was longer with 0.75% ropivacaine. No unexpected adverse events were registered, although there was a high incidence (11 of 40) of postdural puncture headache in this study of relatively young patients in whom a 26-gauge Quincke point needle was used.

The high proportion of patients not achieving complete motor block with 0.5 % ropivacaine 3 ml may have implications in terms of a "test dose" as the absence of full motor block may not exclude intrathecal placement of a catheter. Ropivacaine is not currently intended for use in spinal anaesthesia and research work has been restricted to safety analysis.

Extradural analgesia in labour

Two studies [49, 73] have been published, at the time of writing, comparing ropivacaine and bupivacaine in extradural analgesia in labour. The first study [49] compared a loading dose of 10 ml of 0.5 % followed by a top-up of 0.25 % ropivacaine or bupivacaine 10 ml. The other study [73] compared a continuous infusion of 0.25 % ropivacaine with 0.25 % bupivacaine 6–12 ml h^{-1} after a loading dose of 10 ml of this concentration. There was no difference in motor block in both studies, as assessed by the modified Bromage scale. This qualitative assessment may not be sensitive enough to detect differences in intensity of motor block in the segmental block required for analgesia in labour. Ropivacaine provided effective pain relief in labour and there was no difference in mode of delivery or neonatal outcome.

Extradural anaesthesia for Caesarean section

Ropivacaine 0.5 % has been compared with 0.5 % bupivacaine in extradural anaesthesia for Caesarean section. In one study [21] a standard dose of ropivacaine or bupivacaine 150 mg (30 ml) was given, and in another study [29] a mean volume of 23.7 ml of ropivacaine and 23.1 ml of bupivacaine was required to achieve an upper sensory level of block to the sixth thoracic dermatome. Both studies showed no difference in the profile of sensory block, but the duration of motor block with ropivacaine was significantly shorter compared with bupivacaine. Neonatal outcome and umbilical cord blood-gas tensions were similar. No detrimental effect has been observed with ropivacaine in extradural anaesthesia for Caesarean section on the uteroplacental or fetal circulations, as assessed by colour Doppler ultrasound [6].

Safety analysis

More than 2500 patients have now received ropivacaine in closely monitored controlled clinical trials evaluating the efficacy and safety of the drug. Details of all adverse events have been recorded and investigated. The reported incidences of serious adverse events that occurred in double-blind studies were lower during surgery, labour and Caesarean section with ropivacaine than with bupivacaine. None of the adverse events was considered to be drug related. Inadvertent i.v. injection of ropivacaine 75–200 mg occurred in five patients. None showed signs of cardiotoxicity. Convulsions occurred in one patient who received ropivacaine 200 mg intravascularly during an axillary brachial plexus block procedure. Prompt appropriate treatment led to full recovery within 2 min [personal communication, Dr Dag Selander].

Conclusions

Ropivacaine is an effective long-acting local anaesthetic and the first produced as a pure enantiomer. The sensory block provided by ropivacaine is similar to that produced by an equivalent dose of bupivacaine in extradural and peripheral nerve block. The motor block produced by ropivacaine is slower in onset, less intense and shorter in duration than that after an equivalent dose of bupivacaine. Motor block intensifies as the dose of ropivacaine is increased in extradural anaesthesia. This, together with its lower toxicity compared with bupivacaine, enables ropivacaine to be used for surgical anaesthesia in concentrations up to 1 %.

Ropivacaine is the first local anaesthetic drug to have been evaluated definitively, at an early stage in its development, as an analgesic for continuous extradural infusion. The profile of block with low doses of ropivacaine in terms of its greater sensory–motor separation and higher clearance than bupivacaine make it suitable for such use, although current experience is limited to 24 h. The clinical place of ropivacaine in extradural analgesia by continuous infusion during labour and the post-operative period has yet to be determined, but research to date suggests that ropivacaine offers distinct advantages over bupivacaine—the current local anaesthetic drug of choice.

Acknowledgement

The help given by Professor J. A. W. Wildsmith, University of Dundee, in the preparation of this manuscript is gratefully acknowledged.

References

1. Aberg G. Toxicological and local anaesthetic effects of optically active isomers of two local anaesthetic compounds. *Acta Pharmacologica et Toxicologica* 1972; **31**: 273–286.
2. Aberg G, Dhuner KG, Sydnes G. Studies on the duration of local anaesthesia: Structure/activity relationships in a series of homologous local anaesthetics. *Acta Pharmacologica et Toxicologica* 1977; **41**: 432–434.
3. Af Ekenstam B, Egner B, Petersson G. Local anaesthetics: 1. *N*-alkyl pyrrolidine and *N*-alkyl piperidine carboxylic amides. *Acta Chemica Scandinavica* 1957; **11**: 1183–1190.
4. Af Ekenstam B, Egner B, Ulfendahl K, Dhuner KG, Oljelund O. Trials with carbocaine, a new local anaesthetic agent. *British Journal of Anaesthesia* 1956; **28**: 503–506.
5. Akerman B, Hellberg IB, Trossvik C. Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103). *Acta Anaesthesiologica Scandinavica* 1988; **32**: 571–578.
6. Alahuhta S, Rasanen J, Jouppila P, Kangas-Saarela T, Jouppila R, Westerling P, Hollmen AI. The effects of epidural ropivacaine and bupivacaine for Cesarean section on uteroplacental and fetal circulation. *Anesthesiology* 1995; **83**: 23–32.
7. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979; **51**: 285–287.

8. Arlock P. Actions of three local anaesthetics: lidocaine, bupivacaine and ropivacaine on guinea pig papillary muscle sodium channels (*V*(max)). *Pharmacology and Toxicology* 1988; **63**: 96–104.
9. Arthur GR, Feldman HS, Covino BG. Comparative pharmacokinetics of bupivacaine and ropivacaine, a new amide local anesthetic. *Anesthesia and Analgesia* 1988; **67**: 1053–1058.
10. Axelsson K, Hallgren S, Widman B, Olstrin P. A new method for measuring motor block in the lower extremities. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 72–78.
11. Bader AM, Datta S, Flanagan H, Covino BG. Comparison of bupivacaine- and ropivacaine-induced conduction blockade in the isolated rabbit vagus nerve. *Anesthesia and Analgesia* 1989; **68**: 724–727.
12. Brockway MS, Bannister J, McClure JH, McKeown D, Wildsmith JAW. Comparison of extradural ropivacaine and bupivacaine. *British Journal of Anaesthesia* 1991; **66**: 31–37.
13. Bromage PR. A comparison of the hydrochloride and carbon dioxide salt of lidocaine and prilocaine in epidural analgesia. *Acta Anaesthesiologica Scandinavica* 1965 (Suppl. XVI): 55–69.
14. Brown DL, Carpenter RL, Thompson GE. Comparison of 0.5% ropivacaine and 0.5% bupivacaine for epidural anesthesia in patients undergoing lower-extremity surgery. *Anesthesiology* 1990; **72**: 633–636.
15. Calvey TN. Chirality in anaesthesia. *Anaesthesia* 1992; **47**: 93–94.
16. Cederholm I, Akerman B, Evers H. Local analgesic and vascular effects of intradermal ropivacaine and bupivacaine in various concentrations with and without addition of adrenaline in man. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 322–327.
17. Cederholm I, Anskar S, Bengtsson M. Sensory, motor, and sympathetic block during epidural analgesia with 0.5% and 0.75% ropivacaine with and without epinephrine. *Regional Anesthesia* 1994; **19**: 18–33.
18. Cederholm I, Evers H, Lofstrom JB. Effect of intradermal injection of saline or a local anaesthetic agent on skin blood flow—a methodological study in man. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 208–215.
19. Cederholm I, Evers H, Lofstrom JB. Skin blood flow after intradermal injection of ropivacaine in various concentrations with and without epinephrine evaluated by laser Doppler flowmetry. *Regional Anesthesia* 1992; **17**: 322–328.
20. Concepcion M, Arthur GR, Steele SM, Bader AM, Covino BG. A new local anesthetic, ropivacaine. Its epidural effects in humans. *Anesthesia and Analgesia* 1990; **70**: 80–85.
21. Datta S, Camann W, Bader A, VanderBurgh L. Clinical effects and maternal and fetal plasma concentrations of epidural ropivacaine versus bupivacaine for cesarean section. *Anesthesiology* 1995; **82**: 1346–1352.
22. Duthie AM, Wyman JB, Lewis GA. Bupivacaine in labour: its use in lumbar extradural analgesia. *Anaesthesia* 1968; **23**: 20–26.
23. Ekblom L, Widman B. A comparison of the properties of LAC-43, prilocaine and mepivacaine in extradural anaesthesia. *Acta Anaesthesiologica Scandinavica* 1966 (Suppl. XXI): 33–43.
24. Erichsen CJ, Vibits H, Dahl JB, Kehlet H. Wound infiltration with ropivacaine and bupivacaine for pain after inguinal herniotomy. *Acta Anaesthesiologica Scandinavica* 1995; **39**: 67–70.
25. Federsel H, Jaksch P, Sandberg R. An efficient synthesis of a new, chiral 2′, 6′-pipecoloxylidide local anaesthetic agent. *Acta Chemica Scandinavica* 1987; **B41**: 757–761.
26. Feldman HS, Arthur GR, Covino BG. Comparative systemic toxicity of convulsant and supraconvulsant doses of intravenous ropivacaine, bupivacaine, and lidocaine in the conscious dog. *Anesthesia and Analgesia* 1989; **69**: 794–801.
27. Feldman HS, Arthur GR, Pitkanen M, Hurley R, Doucette AM, Covino BG. Treatment of acute systemic toxicity after the rapid intravenous injection of ropivacaine and bupivacaine in the conscious dog. *Anesthesia and Analgesia* 1991; **73**: 373–384.
28. Feldman HS, Covino BG. Comparative motor-blocking effects of bupivacaine and ropivacaine, a new amino amide local anesthetic, in the rat and dog. *Anesthesia and Analgesia* 1988; **67**: 1047–1052.
29. Griffin RP, Reynolds F. Extradural anaesthesia for Caesarean section: A double-blind comparison of 0.5% ropivacaine with 0.5% bupivacaine. *British Journal of Anaesthesia* 1995; **74**: 512–516.
30. Guinard JP, Nadir B, Carpenter RL, Owens BD. Original article. Comparison between ropivacaine and bupivacaine after subcutaneous injection in pigs: Cutaneous blood flow and surgical bleeding. *Regional Anesthesia* 1991; **16**: 268–271.
31. Heath ML. Deaths after intravenous regional anaesthesia. *British Medical Journal* 1982; **285**: 913–914.
32. Hickey R, Blanchard J, Hoffman J, Sjovall J, Ramamurthy S. Plasma concentrations of ropivacaine given with or without epinephrine for brachial plexus block. *Canadian Journal of Anaesthesia* 1990; **37**: 878–882.
33. Hickey R, Candido KD, Ramamurthy S, Winnie AP, Blanchard J, Raza SM, Hoffman J, Durrani Z, Masters RW. Brachial plexus block with a new local anaesthetic: 0.5 per cent ropivacaine. *Canadian Journal of Anaesthesia* 1990; **37**: 732–738.
34. Hickey R, Hoffman J, Ramamurthy S. A comparison of ropivacaine 0.5% and bupivacaine 0.5% for brachial plexus block. *Anesthesiology* 1991; **74**: 639–642.
35. Hickey R, Rowley CL, Candido KD, Hoffman J, Ramamurthy S, Winnie AP. A comparative study of 0.25% ropivacaine and 0.25% bupivacaine for brachial plexus block. *Anesthesia and Analgesia* 1992; **75**: 602–606.
36. Johansson B, Glise H, Hallerback B, Dalman P, Kristoffersson A. Preoperative local infiltration with ropivacaine for postoperative pain relief after cholecystectomy. *Anesthesia and Analgesia* 1994; **78**: 210–214.
37. Kasten GW. High serum bupivacaine concentrations produce rhythm disturbances similar to torsades de pointes in anesthetised dogs. *Regional Anesthesia* 1986; **11**: 20–25.
38. Katz JA, Bridenbaugh PO, Knarr DC, Helton SH, Denson DD. Pharmacodynamics and pharmacokinetics of epidural ropivacaine in humans. *Anesthesia and Analgesia* 1990; **70**: 16–21.
39. Katz JA, Knarr D, Bridenbaugh PO. A double-blind comparison of 0.5% bupivacaine and 0.75% ropivacaine administered epidurally in humans. *Regional Anesthesia* 1990; **15**: 250–252.
40. Katz JA, Sehlhorst CS, Thompson GA, Denson DD, Coyle D, Bridenbaugh PO. Pharmacokinetics of intravenous and epidural ropivacaine in the Rhesus monkey. *Biopharmaceutics and Drug Disposition* 1993; **14**: 579–588.
41. Kerkkamp HEM, Gielen MJM. Cardiovascular effects of epidural local anaesthetics. Comparison of 0.75% bupivacaine and 0.75% ropivacaine, both with adrenaline. *Anaesthesia* 1991; **46**: 361–365.
42. Kerkkamp HEM, Gielen MJM, Edstrom HH Comparison of 0.75% ropivacaine with epinephrine and 0.75% bupivacaine with epinephrine in lumbar epidural anesthesia. *Regional Anesthesia* 1990; **15**: 204–207.
43. Kopacz DJ, Carpenter RL, Mackey DC. Effect of ropivacaine on cutaneous capillary blood flow in pigs. *Anesthesiology* 1989; **71**: 69–74.
44. Kopacz DJ, Emanuelsson BM, Thompson GE, Carpenter RL, Stephenson CA. Pharmacokinetics of ropivacaine and bupivacaine for bilateral intercostal blockade in healthy male volunteers. *Anesthesiology* 1994; **81**: 1139–1148.
45. Lanz E, Theiss D, Kellner G, Zimmer M, Staudte H. Assessment of motor blockade during epidural anesthesia. *Anesthesia and Analgesia* 1983; **62**: 889–893.
46. Lee A, Fagan D, Lamont M, Tucker GT, Halldin M, Scott DB. Disposition kinetics of ropivacaine in humans. *Anesthesia and Analgesia* 1989; **69**: 736–738.
47. Luduena FP. Duration of local anesthesia. *Annual Review of Pharmacology* 1969; **9**: 503–520.
48. Marx GF. Cardiotoxicity of local anesthetics—the plot thickens. *Anesthesiology* 1984; **60**: 3–5.
49. McCrae AF, Jozwiak H, McClure JH. Comparison of ropivacaine and bupivacaine in extradural analgesia for the relief of pain in labour. *British Journal of Anaesthesia* 1995; **74**: 261–265.
50. Moller R, Covino BG. Cardiac electrophysiologic properties of bupivacaine and lidocaine compared with those of ropivacaine, a new amide local anesthetic. *Anesthesiology* 1990; **72**: 322–329.

51. Moller RA, Covino BG. Effect of progesterone on the cardiac electrophysiologic alterations produced by ropivacaine and bupivacaine. *Anesthesiology* 1992; 77: 735–741.
52. Morishima HO, Pedersen H, Finster M, Hiraoka H, Tsuji A, Feldman HS, Arthur GR, Covino BG. Bupivacaine toxicity in pregnant and non-pregnant ewes. *Anesthesiology* 1985; **63**: 134–139.
53. Morrison LMM, Emanuelsson BM, McClure JH, Pollok AJ, McKeown DW, Brockway M, Jozwiak H, Wildsmith JAW. Efficacy and kinetics of extradural ropivacaine: Comparison with bupivacaine. *British Journal of Anaesthesia* 1994; 72: 164–169.
54. Nakamura K, Toda H, Kakuyama M, Nishiwada M, Yamamoto M, Hatano Y, Mori K. Direct vascular effect of ropivacaine in femoral artery and vein of the dog. *Acta Anaesthesiologica Scandinavica* 1993; 37: 269–273.
55. Nancarrow C, Rutten AJ, Runciman WG, Mather LE, Carapetis RJ, McLean CF, Hipkins SF. Myocardial and cerebral drug concentrations and the mechanisms of death after fatal intravenous doses of lidocaine, bupivacaine, and ropivacaine in the sheep. *Anesthesia and Analgesia* 1989; **69**: 276–283.
56. Niesel HC, Eilingsfeld T, Hornung M, Kaiser H. Ropivacain 1% versus bupivacain 0.75% ohne vasokonstriktor. Vergleichende untersuchung zur epiduralanasthesie bei orthopadischen eingriffen. Plain ropivacaine 1% versus bupivacaine 0.75% in epidural anaesthesia. A comparative study in orthopaedic surgery. *Anaesthesist* 1993; **42**: 605–611.
57. Niesel HC, Eilingsfeld T, Kaiser H, Klimpel L. Ropivacain zur periduralanasthesia. Untersuchungen zur dosiswirkungsrelation bei orthopadischen eingriffen. Ropivacaine in epidural analgesia. Dose-response study in orthopaedic surgery. *Anaesthetist—Regional Anaesthesie* 1990; 13: 73–77.
58. Nolte H, Fruhstorfer H, Edstrom HH. Local anesthetic efficacy of ropivacaine (LEA 103) in ulnar nerve block. *Regional Anesthesia* 1990; **15**: 118–124.
59. Nydahl P, Axelsson K, Hallgren S, Larsson P, Leissner P, Philipson L. Evaluation of motor blockade by isometric force measurement and electromyographic recording during epidural anaesthesia—a methodological study. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 477–484.
60. Pitkanen M, Covino BG, Feldman HS, Arthur GR. Chronotropic and inotropic effects of ropivacaine, bupivacaine, and lidocaine in the spontaneously beating and electrically paced isolated, perfused rabbit heart. *Regional Anesthesia* 1992; **17**: 183–192.
61. Reiz S, Haggmark S, Johansson G, Nath S. Cardiotoxicity of ropivacaine—A new amide local anaesthetic agent. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 93–98.
62. Reiz S, Nath S. Cardiotoxicity of local anaesthetic agents. *British Journal of Anaesthesia* 1986; **58**: 736–746.
63. Rosenberg PH, Heinonen E. Differential sensitivity of A and C nerve fibres to long-acting amide local anaesthetics. *British Journal of Anaesthesia* 1983; **55**: 163–167.
64. Rosenberg PH, Kytta J, Alila A. Absorption of bupivacaine, etidocaine, lignocaine and ropivacaine into n-heptane, rat sciatic nerve, and human extradural and subcutaneous fat. *British Journal of Anaesthesia* 1986; **58**: 310–314.
65. Rubin AP, Lawson DIF. A controlled trial of bupivacaine: a comparison with lignocaine. *Anaesthesia* 1968; **23**: 327–330.
66. Rutten AJ, Mather LE, Nancarrow C, Sloan PA, McLean CF. Cardiovascular effects and regional clearances of intravenous ropivacaine in sheep. *Anesthesia and Analgesia* 1990; **70**: 577–582.
67. Rutten AJ, Nancarrow C, Mather LE, Ilsley AH, Runciman WB, Upton RN. Hemodynamic and central nervous system effects of intravenous bolus dose of lidocaine, bupivacaine, and ropivacaine in sheep. *Anesthesia and Analgesia* 1989; **69**: 291–299.
68. Santos AC, Arthur GR, Pedersen H, Morishima HO, Finster M, Covino BG. Systemic toxicity of ropivacaine during ovine pregnancy. *Anesthesiology* 1991; **75**: 137–141.
69. Santos AC, Arthur GR, Wlody D, De Armas P, Morishima HO, Finster M. Comparative systemic toxicity of ropivacaine and bupivacaine in nonpregnant and pregnant ewes. *Anesthesiology* 1995; **82**: 734–740.
70. Scott DB, Lee A, Fagan D, Bowler GMR, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesthesia and Analgesia* 1989; **69**: 563–569.
71. Scott DB, McClure JH, Giasi RM, Seo J, Covino BG. Effects of concentration of local anaesthetic drugs in extradural blockade. *British Journal of Anaesthesia* 1980; **52**: 1033–1037.
72. Steel GC, Dawkins CJM. Extradural lumbar block with bupivacaine (Marcain: LAC-43). *Anaesthesia* 1968; **23**: 14–19.
73. Stienstra R, Jonker TA, Bourdrez P, Kuijpers JC, Van Kleef JW, Lundberg U. Ropivacaine 0.25% versus bupivacaine 0.25% for continuous epidural analgesia in labor: A double-blind comparison. *Anesthesia and Analgesia* 1995; **80**: 285–289.
74. Terasaki T, Pardridge WM, Denson DD. Differential effect of plasma protein binding on its in-vivo transfer into brain and salivary gland of rats. *Journal of Pharmacology and Experimental Therapeutics* 1986; **239**: 724–729.
75. Tucker GT. Pharmacokinetics of local anaesthetics. *British Journal of Anaesthesia* 1986; **58**: 717–731.
76. Van Kleef JW, Veering BT, Burm AGL. Spinal anesthesia with ropivacaine: A double-blind study on the efficacy and safety of 0.5% and 0.75% solutions in patients undergoing minor lower limb surgery. *Anesthesia and Analgesia* 1994; **78**: 1125–1130.
77. Vanhoutte F, Vereecke J, Verbeke N, Carmeliet E. Stereoselective effects of enantiomers of bupivacaine on the electrophysiological properties of the guinea-pig papillary muscle. *British Journal of Pharmacology* 1991; **103**: 1275–1281.
78. Veering BT, Burm AGL, Van Kleef JW, Hennis PJ, Spierdijk J. Epidural anesthesia with bupivacaine: effects of age on neural blockade and pharmacokinetics. *Anesthesia and Analgesia* 1987; **66**: 589–594.
79. Watt MJ, Ross DM, Atkinson RS. A double-blind trial of bupivacaine and lignocaine: Latency and duration in extradural blockade. *Anaesthesia* 1968; **23**: 311–373.
80. Watt MJ, Ross DM, Atkinson RS. Clinical trial of bupivacaine. *Anaesthesia* 1968; **23**: 2–13.
81. Whitehead E, Arrigoni B, Bannister J. An open study of ropivacaine in extradural anaesthesia. *British Journal of Anaesthesia* 1990; **64**: 67–71.
82. Widman B. Clinical trial of a new local anaesthetic (LAC-43) with the aid of the pinprick and ninhydrin methods in finger blocks. *Acta Anaesthesiologica . Scandinavica* 1964; **8**: 219–226.
83. Wildsmith JAW, Brown DT, Paul D, Johnson S. Structure-activity relationships in differential nerve block at high and low frequency stimulation. *British Journal of Anaesthesia* 1989; **63**: 444–452.
84. Wolff AP, Hasselstrom L, Kerkkamp HE, Gielen MJ. Extradural ropivacaine and bupivacaine in hip surgery. *British Journal of Anaesthesia* 1995; **74**: 458–460.
85. Wood MB, Rubin AP. A comparison of epidural 1% ropivacaine and 0.75% bupivacaine for lower abdominal gynecologic surgery. *Anesthesia and Analgesia* 1993; **76**: 1274–1278.
86. Zaric D, Axelsson K, Nydahl PA, Philipson L, Larsson P, Jansson JR. Sensory and motor blockade during epidural analgesia with 1%, 0.75%, and 0.5% ropivacaine—A double-blind study. *Anesthesia and Analgesia* 1991; **72**: 509–515.
87. Zaric D, Axelsson K, Philipson L, Nydahl PA, Larsson P, Jansson JR, Leissner P. Blockade of the abdominal muscles measured by EMG during lumbar epidural analgesia with ropivacaine—A double-blind study. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 274–280.
88. Zaric D, Nydahl P, Philipson L, Samuelsson L, Heierson A, Axelsson K. The effect of continuous lumbar epidural infusion of ropivacaine (0.1%, 0.2% and 0.3%) and 0.25% bupivacaine on sensory and motor blockade in volunteers:- a double-blind study. *Regional Anesthesia* 1995; in press.

British Journal of Anaesthesia 1996; **76**: 308–309

SHORT COMMUNICATIONS

Dose of propofol for laryngeal mask airway insertion in children: effect of premedication with midazolam

R. A. MARTLEW, G. MEAKIN, R. WADSWORTH, A. SHARPLES AND R. D. BAKER

Summary

We determined the dose–response curves and effective doses of propofol for insertion of the laryngeal mask airway (LMA) in 50 unpremedicated children and in 60 children premedicated with midazolam, aged 3–12 yr. One of several doses of propofol was administered i.v. over 15 s to groups of 10 children, and conditions for LMA insertion were assessed at 60 s. The dose–response curves were parallel ($P = 0.94$), but the curve for premedicated children was shifted significantly to the left of that for unpremedicated children and propofol requirements were reduced by one-third ($P < 0.0001$). The doses required for satisfactory LMA insertion in 50% and 90% of unpremedicated patients (ED_{50}, ED_{90}) (95% confidence interval) were 3.8 (3.4–4.2) mg kg^{-1} and 5.4 (4.7–6.8) mg kg^{-1}, respectively; those for premedicated patients were 2.6 (2.2–2.8) mg kg^{-1} and 3.6 (3.2–4.3) mg kg^{-1}, respectively. (*Br. J. Anaesth.* 1996; **76**: 308–309)

Key words

Anaesthesia, paediatric. Anaesthetics i.v., propofol. Premedication, midazolam. Equipment, masks anaesthesia. Children.

Insertion of the laryngeal mask airway (LMA) soon after induction of anaesthesia is facilitated by the use of propofol, which depresses pharyngeal and laryngeal reflexes. The results of a previous study in children suggested that the dose of propofol required for insertion of the LMA may be greater than that for acceptance of a face mask [1]; however, there have been no formal studies to determine dose–response curves or effective doses. Oral midazolam is an effective sedative premedicant in children [2], which is synergistic with propofol [3] and may reduce the dose required for LMA insertion. Accordingly, the aims of this study were to determine the dose–response curves and effective doses of propofol for LMA insertion in unpremedicated and midazolam-premedicated children.

Methods and results

The study was approved by the Local Ethics Committee and written consent was obtained from the parents. We studied 110 children, ASA I or II, aged 3–12 yr and undergoing general anaesthesia for minor surgical procedures. Children with body weights outside the third to 97th centiles, and those with neuromuscular disease, anatomical abnormalities of the airway or asthma were excluded. Subjects were allocated randomly to one of two main groups to receive either no premedication ($n = 50$) or premedication with oral midazolam 0.5 mg kg^{-1}, 30–60 min before anaesthesia ($n = 60$).

Before induction of anaesthesia, a pulse oximeter and ECG monitor were attached and children were allocated randomly to subgroups of 10, to receive one of several predetermined doses of propofol: five groups of unpremedicated patients received 3.0, 3.4, 3.9, 4.4 or 5.0 mg kg^{-1}, while six groups of premedicated patients received 2.2, 2.6, 3.0, 3.4, 3.9 or 4.4 mg kg^{-1}. To reduce pain on injection, lignocaine 10 mg was added to each 100 mg of propofol. Propofol was administered over 15 s via an i.v. cannula sited on the back of one hand, following which the lungs were ventilated with 100% oxygen for 60 s before attempting insertion of the LMA as described in the manufacturer's instructions [4]. Conditions for LMA insertion were assessed by an anaesthetist who was unaware of the dose of propofol and the type of premedication given. Conditions were considered satisfactory if the jaw was relaxed, there was no coughing, gagging, swallowing or laryngeal spasm, and minimal or no limb movement. If conditions were considered to be unsatisfactory, anaesthesia was deepened with further increments of propofol, or an inhalation agent, or both, until the LMA was tolerated. Oscillometric arterial pressure measurement was commenced after insertion of the LMA and continued at 3-min intervals throughout surgery.

Dose–response data were analysed by probit analysis. Maximum likelihood estimates of model variables were found using a Fortran program written by one of the authors (R.D.B.); numerical algorithms group (NAG) routines were used for functional minimization. The slopes and intercepts

---

ROBERT A. MARTLEW, MB, CHB, FRCA, GEORGE MEAKIN, MD, FRCA, DA, RICHARD WADSWORTH, BSC, MB, BCHIR, FRCA, ANDREW SHARPLES, MB, CHB, FRCA, University Department of Anaesthesia, Royal Manchester Children's Hospital, Pendlebury, Manchester M27 4HA. ROSE D. BAKER, MA, PHD, CSTAT, CMATH, FIMA, Department of Mathematics, University of Salford, Salford M5 4WT.

Accepted for publication: September 5, 1995.

Correspondence to G.M.

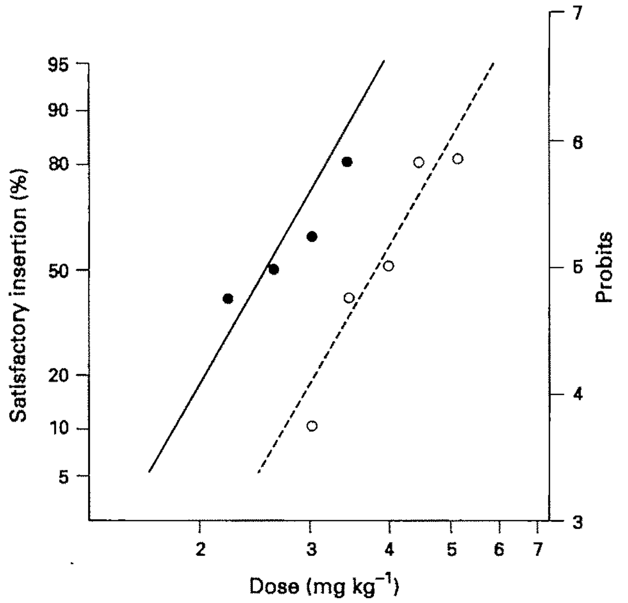


Figure 1 Log dose–probit response curves of propofol for LMA insertion in unpremedicated (○) and midazolam-premedicated (●) children. The points along the lines represent mean responses from subgroups of 10 patients. Only four of the six points can be shown for the midazolam group, as satisfactory LMA insertion conditions were obtained in 100% of patients who received the two higher doses (probit = ∞).

of the dose–response lines for unpremedicated and premedicated patients were compared using analysis of deviance, and 95% confidence intervals on ED values were found using the profile likelihood function [5]. Statistical differences in patient data were assessed by one-way ANOVA.

There were no significant differences in mean ages and weights of the children in the various propofol dose groups, or in the times from administration of midazolam to induction of anaesthesia in the groups of premedicated children. Log dose–probit response curves for unpremedicated and midazolam-premedicated children are shown in figure 1. The equations of the lines were probit = 3.8 log dose −0.09 and probit = 3.8 log dose −3.7, respectively. The slopes of the lines did not differ significantly ($P = 0.94$), but the curve for premedicated children was significantly to the left of that for unpremedicated children ($P < 0.0001$).

The effective doses of propofol for LMA insertion in 50% and 90% of unpremedicated children (ED_{50}, ED_{90}) (95% confidence intervals) were 3.8 (3.4–4.2) mg kg^{-1} and 5.4 (4.7–6.8) mg kg^{-1}, respectively; those for premedicated children were 2.6 (2.2–2.8) mg kg^{-1} and 3.6 (3.2–4.3) mg kg^{-1}, respectively. The differences in effective doses between unpremedicated and midazolam-premedicated children were highly significant ($P < 0.001$).

Comment

The results of the present study confirm that induction of anaesthesia with propofol allowed early insertion of the LMA in paediatric practice. The effective dose of propofol for insertion of the LMA in 90% of unpremedicated children exceeded 5 mg kg^{-1}, but this was reduced to less than 4 mg kg^{-1} after premedication with midazolam. our results support the suggestion that the dose of propofol required for insertion of the LMA is greater than that required for acceptance of a face mask in children [1] and may be proportionally greater than that required for LMA insertion in adults [6, 7]. Increased induction requirements for propofol in children may be explained by a larger central volume of distribution of the drug [8, 9] and a greater cardiac output per kilogram body weight, which should result in a lower peak concentration of propofol in the blood perfusing the brain after bolus injection.

The ED_{90} propofol dose of more than 5.0 mg kg^{-1} in unpremedicated children exceeds previous recommendations for induction of anaesthesia. As propofol is known to produce cardiorespiratory depression in children at doses considerably less than this [10], hypotension or prolonged apnoea may be a problem. However, during the study we did not observe any differences in the incidence of cardiorespiratory side effects between the low and high dose propofol groups.

References

1. Allsop E, Innes P, Jackson M, Cunliffe M. Dose of propofol required to insert the laryngeal mask airway in children. *Paediatric Anaesthesia* 1995; 5: 47–51.
2. McCluskey A, Meakin GH. Oral administration of midazolam as a premedicant for paediatric day-case anaesthesia. *Anaesthesia* 1994; 49: 782–785
3. Short TG, Chiu PT. Propofol and midazolam act synergistically in combination. *British Journal of Anaesthesia* 1991; 67: 539–545
4. Brain AIJ. In: *The Intavent Laryngeal Mask Instruction Manual*, 2nd Edn. Henley on Thames: Intavent, 1991; 7
5. Aitkin M, Anderson D, Francis B, Hinde J. *Statistical Modelling in GLIM*. Oxford: Clarendon Press, 1989; 192–194.
6. Brown GW, Patel N, Ellis FR. Comparison of propofol and thiopentone for laryngeal mask insertion. *Anaesthesia* 1991; 46: 771–772.
7. Blake DW, Dawson P, Donnan G, Bjorksten A. Propofol induction for laryngeal mask airway insertion: dose requirement and cardiorespiratory effects. *Anaesthesia and Intensive Care* 1992; 20: 479–483.
8. Saint-Maurice C, Cockshott ID, Douglas EJ, Richard MO, Harmey JL. Pharmacokinetics of propofol in young children after a single dose. *British Journal of Anaesthesia* 1989; 63: 667–670.
9. Marsh B, White M, Morton N, Kenny GNC. Pharmacokinetic model driven infusion of propofol in children. *British Journal of Anaesthesia* 1991; 67: 41–48.
10. Morton NS, Johnston G, White M, Marsh BJ. Propofol in paediatric anaesthesia. *Paediatric Anaesthesia* 1992; 2: 89–97.

British Journal of Anaesthesia 1996; **76**: 310–312

Comparison of i.v. and s.c. diamorphine infusions for the treatment of acute pain in children

D. SEMPLE, L. A. ALDRIDGE AND E. DOYLE

Summary

We have compared the i.v. and s.c. routes of administration for diamorphine infusions in children undergoing abdominal surgery. Subjects received general anaesthesia with extradural block and diamorphine up to 20 μg kg^{-1} h^{-1} after operation. There were no differences between the groups in diamorphine consumption, pain scores or incidence of side effects. The s.c. route appeared to be as effective and safe as the i.v. route for administration of diamorphine infusions in children undergoing elective surgery. (*Br. J. Anaesth.* 1996; **76**: 310–312)

Key words

Analgesia, paediatric. Analgesic techniques, i.v. Analgesic techniques, s.c. Analgesics opioid, diamorphine. Pain, postoperative.

The use of i.v. opioid infusions to treat postoperative pain in children is a common and effective analgesic technique [1]. It requires a dedicated i.v. cannula for opioid administration in addition to one for i.v. fluids and drugs. Alternatively, the same cannula may be used for both fluids and opioid administration if an antireflux valve is used. The option of a second i.v. cannula is not always available, particulary in infants, while antireflux valves are expensive and make the infusion site bulky and difficult to nurse.

An alternative route of administration for opioid infusions which does not have these disadvantages is the s.c. route. This is used extensively in terminal and chronic pain and has also been described for the management of acute pain in adults [2]. The efficacy of s.c. infusions in children has been demonstrated recently [3]. For this technique to become widespread and accepted it must be shown to be as effective as the i.v. route with the same or a lower incidence of side effects. The i.v. and s.c. routes of administration have not been compared in children. This study was designed to compare these two routes in children undergoing abdominal surgery. On the basis of previous work using similar methodology [4] the power calculated for the study was that it would have a 90 % chance of detecting differences between the groups which were significant at the 5 % level.

Methods and results

The study was approved by the local Ethics Committee and written informed parental consent was obtained for each subject. We studied 30 children, aged 6 months to 11 yr, undergoing abdominal surgery. Exclusion criteria included contraindications to extradural block, significant hepatic or renal impairment, and significant mental handicap making assessment of pain difficult. Patients were premedicated with EMLA cream and anaesthesia was induced with propofol 3–4 mg kg^{-1} and atracurium 0.5 mg kg^{-1}. After tracheal intubation, the lungs were ventilated with 0.5–2 % halothane and 70 % nitrous oxide in oxygen. Patients were then turned to the right lateral position and an extradural catheter placed at an appropriate dermatomal level for the proposed surgery. Extradural block was provided with 0.25 % bupivacaine 1 ml kg^{-1} with adrenaline 1/200000 (maximum 20 ml) in divided doses. At the end of surgery, neuromuscular block was antagonized and the trachea extubated.

Patients were allocated randomly to receive either an i.v. or an s.c. infusion of diamorphine after operation. In the i.v. group (group IV), a second 22-gauge cannula was sited on the same side as the cannula used for induction. In the s.c. group (group SC), a 22-gauge cannula was sited s.c. over the deltoid muscle on the same side as the i.v. cannula.

In group IV the solution used consisted of diamorphine 1 mg kg^{-1} diluted in 50 ml of 0.9 % saline to give a concentration of 20 μg kg^{-1} ml^{-1}. This was commenced at a rate of 1 ml h^{-1} (20 μg kg^{-1} h^{-1}). In group SC the solution used consisted of diamorphine 1 mg kg^{-1} diluted in 20 ml of 0.9 % saline to give a concentration of 50 μg kg^{-1} ml^{-1}. This was commenced at 0.4 ml h^{-1} (20 μg kg^{-1} h^{-1}). Diamorphine infusions were started in the recovery area. Infusions were delivered using a Graseby MS2000 pump.

After operation we used a monitoring regimen described previously [5]. Patients breathed air and had continuous monitoring of arterial oxygen saturation. We measured hourly values of ventilatory frequency, pain score, sedation score, nausea score and volume of diamorphine infused. Diamorphine was infused at a maximum rate of 20 μg kg^{-1} h^{-1} and boluses of diamorphine 50 μg kg^{-1} were available if required.

Pain was assessed by a small group of experienced paediatric surgical nurses and measured using a

---

D. SEMPLE, FRCA, L. A. ALDRIDGE, FRCA, E. DOYLE, FRCA, Department of Anaesthesia, Royal Hospital for Sick Children, Sciennes Road, Edinburgh EH9 1LB. Accepted for publication: September 6, 1995.

Correspondence to E.D.

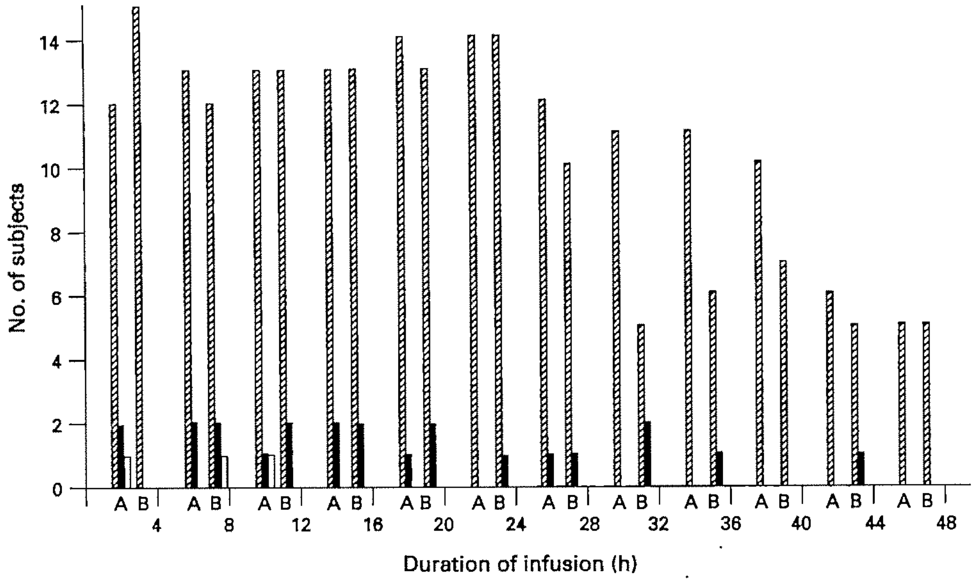


Figure 1 Comparison of pain scores (▨ = 1, ■ = 2, □ = 3) in groups IV (A) and SC (B).

four-point scale described previously [6]: 1 = no pain; 2 = mild pain; 3 = moderate pain; 4 = severe pain. Children were not wakened from sleep for assessments unless the nurse suspected excessive sedation. Sedation was scored using a four-point scale: 0 = eyes open spontaneously; 1 = eyes open in response to speech; 2 = eyes open when shaken; 3 = unrousable. Vomiting was scored on a three-point scale: 0 = none; 1 = vomited once in the last hour; 2 = vomited more than once in the last hour.

Infusions were discontinued when there was a consistent decline in diamorphine requirements and patients were able to take oral analgesics. Results were analysed using the Student's *t* test for parametric data and the Mann–Whitney *U* test for non-parametric data.

The two groups were similar in characteristics (mean age 36 months in group IV and 33 months in group SC), surgical procedures (eight gastrointestinal, two pyeloplasties, three nephrectomies and two ureteric reimplantations in group IV and six gastrointestinal, two pyeloplasties, five nephrectomies and two ureteric reimplantations in group SC) and duration of surgery (median 80 min in group IV and 65 min in group SC).

The duration of infusion analgesia (median 41 h in group IV and 39 h in group SC) and total diamorphine consumption (median 680 (range 220–1120) $\mu g\,kg^{-1}$ in group IV and 600 (260–1160) $\mu g\,kg^{-1}$ in group SC) did not differ significantly between the groups. To assess efficacy, we compared the median total pain scores in each group during each 4-h period after operation. There were no significant differences between the groups at any point (fig. 1). Two children in group IV and three children in group SC received one supplementary bolus of diamorphine for inadequate analgesia at the maximum infusion rate.

There were no significant differences between the groups in the incidence of vomiting, excessive sedation or hypoxic episodes. Five patients in group IV and seven patients in group SC vomited. Excessive sedation was defined as a sedation score of 2 or 3; a score of 2 occurred on two occasions in one patient in group IV and on seven occasions in two patients in group SC. All episodes of excessive sedation occurred during the first postoperative day while the infusion rate was 20 $\mu g\,kg^{-1}\,h^{-1}$. A hypoxic episode was defined as Sp_{O_2} less than 94%; there were 14 episodes in four patients in group IV and 18 episodes in five patients in group SC.

Two cannulae in group IV and no cannulae in group SC needed to be replaced during the diamorphine infusion.

Comment

We have observed that the s.c. route of administration is as effective as the i.v. route for infusion of diamorphine in children after elective surgery. Although s.c. administration has been shown to provide analgesia [3] in children, it has not been shown previously to be as effective as the i.v. route.

The fact that equivalent analgesia can be provided by this route with similar doses of diamorphine and no increase in the incidence of side effects suggests that this technique may be useful in children receiving other opioids by infusion. Use of the s.c. route for opioid infusions is likely to reduce the practical difficulties associated with the provision of this form of analgesia in small children. Intermittent injections of opioid through an indwelling s.c. cannula may be used instead of an infusion but, in common with intermittent i.m. injections, may result in periods of unrelieved pain alternating with episodes of sedation or nausea induced by high plasma concentrations of opioid after bolus dose administration. There was no blinding of observers to the type of infusion used in this study and there is the possibility of bias in the recordings. Furthermore the method of pain assessment used (observer scoring) is not as satisfactory as patient self-report and must be considered to be a relatively insensitive discriminator between analgesic regimens.

It should be noted that the subjects in this study were elective normovolaemic patients. The s.c. route would be contraindicated in patients with or at risk of developing poor peripheral perfusion when there would be a risk of accumulation of opioid at the infusion site resulting in poor analgesia and subsequent absorption of this depot to give the equivalent of a large uncontrolled bolus of opioid.

References

1. Pounder DR, Steward DJ. Postoperative analgesia: opioid infusions in infants and children. *Canadian Journal of Anaesthesia* 1992; **39**: 969–974.
2. Hindsholm KB, Bredahl C, Jensen MK, Kidmose L, Herlevsen P, Neilsen FB, Schou Olesen A. Continuous subcutaneous infusion of morphine—an alternative to extradural morphine for postoperative pain relief. *British Journal of Anaesthesia* 1993; **71**: 580–582.
3. McNicol LR. Postoperative analgesia in children using continuous s.c. morphine. *British Journal of Anaesthesia* 1993; **71**: 752–756.
4. Doyle E, Mottart KJ, Marshall C, Morton NS. Comparison of different bolus doses of morphine for patient-controlled analgesia in children. *British Journal of Anaesthesia* 1994; **72**: 160–163.
5. Morton NS. Development of a monitoring prorocol for the safe use of opioids in children. *Paediatric Anaesthesia* 1993; **3**: 179–184.
6. Maunuksela E, Olkkola KT, Korpela R. Measurement of pain in children with self-reporting and behavioural assessment. *Clinical Pharmacology and Therapeutics* 1987; **42**: 137–141.

British Journal of Anaesthesia 1996; **76**: 313–315

Prospective evaluation of pharmacokinetic model-controlled infusion of propofol in adult patients

T. G. SHORT, T. A. LIM AND Y. H. TAM

Summary

We have tested prospectively the algorithm of White and Kenny for pharmacokinetic model-controlled infusion of propofol in 40 healthy Oriental adults. Anaesthesia consisted of a target-controlled infusion of propofol, 70% nitrous oxide and an infusion of alfentanil. For the first 20 patients studied, median performance error was −5%, median absolute performance error 19%, divergence −9% and wobble 6%. The model was revised to minimize the prediction error of the variable set and tested prospectively in another 20 patients. There was a deterioration in performance of the revised model. Performance statistics for the original model in all 40 patients were: median performance error 2% (range −34 to 69%), median absolute performance error 21% (6–69%), divergence −17% (−92 to 49%) and wobble 7% (2–34%). The algorithm was found to perform adequately in our Oriental patient population. (*Br. J. Anaesth.* 1996; **76**: 313–315)

Key words

Anaesthetic techniques, i.v. Drug delivery, computerized. Anaesthetics i.v., propofol, Pharmacokinetics, models.

Successful use of pharmacokinetic model-controlled infusions of drugs in anaesthetic practice requires the use of thoroughly tested algorithms. A recent study of pharmacokinetic model-controlled infusion of propofol in Oriental paediatric patients performed at our institution found this patient group to be described by different pharmacokinetic variables from paediatric patients in a previous study performed by Marsh and colleagues [1, 2]. Their model underestimated propofol requirements in our paediatric patient population by 18%. Because of this pharmacokinetic difference, we decided that the accuracy of a similar algorithm for the infusion of propofol in adult patients should also be tested prospectively in our adult population [3].

Methods and results

We studied 40 ASA I or II adult patients, aged 20–60 yr, undergoing elective surgery expected to last at least 1 h and associated with minimal blood loss. Patients with a preoperative haemoglobin concentration of less than 11 g dl^{-1}, more than 50% above ideal weight or with a contraindication to the use of propofol were excluded. The study was approved by the local Ethics Committee and written informed consent was obtained from all patients.

Patients were premedicated with temazepam 20 mg. Anaesthesia consisted of a pharmacokinetic model-controlled infusion of propofol programmed to rapidly achieve and then maintain a constant concentration in the central compartment. The drug delivery system consisted of an Ohmeda 9000 syringe pump (Medishield, UK) controlled by an IBM compatible computer, as described previously [1]. Rate constants for the three-compartment pharmacokinetic model used were White and Kenny's adaptation of the pharmacokinetic variables of Gepts and colleagues: V_1 (litre kg^{-1}) 0.2280, k_{10} (min^{-1}) 0.1190, k_{12} 0.1120, k_{21} 0.0550, k_{13} 0.0419 and k_{31} 0.0033 [2–4]. The initial target blood concentration was set at 6.0 μg ml^{-1} and then adjusted according to clinical response. Patients also received alfentanil 7 μg kg^{-1} at induction followed by an infusion of 0.25 μg kg^{-1} min^{-1}, 70% nitrous oxide and atracurium if required. The anaesthetic technique was similar to that used by White and Kenny when they prospectively tested this algorithm [4].

After induction of anaesthesia a 22-gauge cannula was placed in a radial artery for blood sampling. At 5–10-min intervals throughout the procedure and at 15–20-min intervals during the first 2 h after cessation of the infusion, 2.0-ml blood samples were obtained. No blood samples were obtained during stepwise increases in propofol concentration. Blood samples were stored and analysed as described previously [1]. Accuracy of the assay was 6.7% at 50 ng ml^{-1} and 4.0% at 3000 ng ml^{-1}.

Performance of the computer-controlled infusion system was assessed using a variance weighted two-stage approach [5]. Performance error was calculated as: performance error $= ((C_{\mathrm{Pmeasured}} - C_{\mathrm{Ppredicted}})/C_{\mathrm{Ppredicted}}) \times 100$, where C_{P} = whole blood concentration of propofol. For each individual, median performance error (MDPE), median absolute per-

---

T. G. SHORT*, MD, FANZCA, FHKAM, T. A. LIM, MB, BS, FRCA, Y. H. TAM, MPHIL, MIEE, Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, and The Prince of Wales Hospital, Hong Kong. Accepted for publication: September 20, 1995.

*Address for correspondence: Department of Anaesthesia and Intensive Care, The Prince of Wales Hospital, Shatin, NT, Hong Kong.

Table 1 Comparisons of initial and revised rate constants for propofol using a three-compartment open model. In part 1, theoretical testing of a revised model suggested it would perform better than the original model. In part 2, prospective evaluation of the revised model found a deterioration in its performance and that the original model would have performed better. Values are variance weighted mean of medians with unweighted range in parentheses. MDPE = Median performance error, MDAPE = median absolute performance error. Analysis of divergence and wobble was not performed for the recovery phase alone because of the small number of blood samples obtained. *Improvement in performance $P < 0.05$; **deterioration in performance $P < 0.01$.

	Part 1		Part 2	
	Original model ($n = 20$)	Theoretical fit of revised model	Prospective testing of revised model ($n = 20$)	Theoretical fit of original model
Infusion phase				
MDPE (%)	−5.4 (−32.5 to 32.0)	−0.7 (−26.8 to 33.6)*	15.4 (−24.9 to 74.0)	8.4 (−33.5 to 69.0)*
MDAPE (%)	19.3 (6.8 to 49.7)	17.8 (4.2 to 45.3)*	25.0 (5.4 to 74.0)	22.8 (6.4 to 69.0)
Divergence (% h^{-1})	−8.6 (−71.3 to 48.9)	2.6 (−31.5 to 83.9)*	−0.5 (−66.7 to 58.6)	−21.3 (−92.4 to 32.5)
Wobble (%)	6.0 (1.8 to 34.4)	8.6 (1.7 to 31.7)**	5.5 (3.0 to 19.0)	8.3 (5.0 to 18.4)**
Early recovery phase				
MDPE (%)	34.9 (3.1 to 117.3)	31.1 (−37.1 to 159.6)*	37.8 (−45.5 to 79.4)	24.3 (−58.4 to 31.4)*
MDAPE (%)	33.1 (12.5 to 117.3)	29.9 (6.0 to 159.6)	37.1 (2.1 to 79.4)	23.5 (4.8 to 58.4)
Both phases				
MDPE (%)	21.6 (−35.7 to 36.4)	19.5 (−26.4 to 61.8)*	25.3 (−22.1 to 74.0)	22.2 (−31.1 to 65.3)*
MDAPE (%)	23.7 (8.7 to 36.4)	19.2 (6.0 to 61.8)*	33.8 (5.3 to 74.0)	22.4 (6.7 to 65.3)
Divergence (% h^{-1})	1.8 (−34.7 to 68)	−6.2 (−27.7 to 60.1)**	2.2 (−30.6 to 84.0)	−15.0 (−75.2 to 68.0)
Wobble (%)	5.9 (1.6 to 5.4)	9.1 (2.3 to 8.2)**	5.8 (3.9 to 16.1)	8.1 (5.0 to 18.4)**

formance error (MDAPE), divergence and wobble were then calculated. Overall performance of the system in the sample population was then assessed as the variance weighted mean of MDPE, MDAPE, divergence and wobble calculated for each individual. Data from the first 20 patients were used to develop an optimized pharmacokinetic variable set with theoretically superior performance when used in our system with a linear least squares regression procedure to find the variable set that would best fit the data by minimizing performance error. The median performance of the revised model for each patient was compared with the median precision of the original model using Wilcoxon's signed rank test. Because the revised variable set was found to fit the data better than the original model for most measures of performance, the revised variable set was then tested prospectively in another 20 patients.

Mean age of the patients was 37 (range 21–58) yr and weight 58 (41–74) kg; 75 % of patients were female and 75 % underwent ventilation of the lungs. Mean duration of propofol infusion was 90 (34–190) min. There were no significant differences in age, weight or sex of patients in the two phases of the study. Operations performed included gynaecological, orthopaedic and general surgery. Blood concentrations required for adequate anaesthesia ranged from 2.0 to 7.0 $\mu g\ ml^{-1}$.

Performance of the initial variable set is shown in table 1. The model was revised and theoretical testing of the revised model found that it fitted the measured blood propofol concentrations significantly better than the original model in terms of MDPE, MDAPE and divergence, but with an increase in wobble. The variable set for the revised model was: V_1 (litre kg^{-1}) 0.2380, k_{10} (min^{-1}) 0.122, k_{12} 0.0406, k_{21} 0.0278, k_{13} 0.048 and k_{31} 0.0045.

Prospective testing of the revised model in another 20 patients found a deterioration in fit compared with its theoretical performance, and that the original model would have fitted these patients better in terms of MDPE but with a small increase in wobble (table 1). It was concluded that the original model based on the variable set of White and Kenny performed best in our patient population.

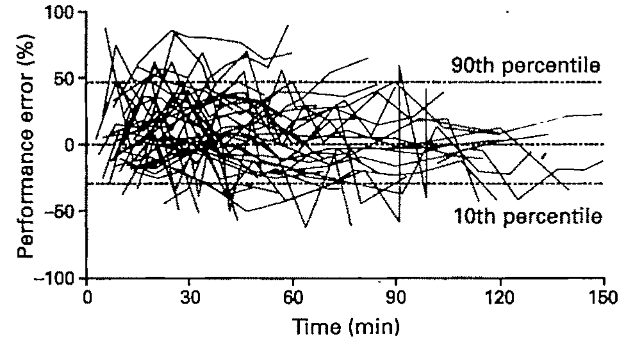


Figure 1 Performance error over time for the infusion phase in all patients using the original model.

Performance errors of the original model using data from all 40 patients in the study are shown as performance errors over time for the infusion phase of the study in figure 1. Performance of the original model in all 40 patients during the infusion phase was MDPE 2 %, MDAPE 21 %, divergence −17.1 % and wobble 7.2 %.

Comment

The pharmacokinetic data set of White and Kenny was found to adequately describe the disposition of propofol during target-controlled infusion in our adult population. This result in Oriental adults is in contrast with our finding in Oriental children [1]. Although it was originally thought that the model for paediatric patients indicated different requirements for propofol in Oriental children, a recent publication of propofol pharmacokinetics during infusion in children from the USA found pharmacokinetic variables which performed similarly in simulations of our paediatric variable set [6].

It is of interest that in our study we used arterial blood sampling, but found the model which had been modified using venous blood samples fitted well. This is probably because arterial sampling is more important when bolus doses are given and multiple early blood samples are obtained, but less important during a prolonged infusion such as was the case in the present study. In general, performance of the model in our patient population, as measured by MDAPE, was better than the performance of similar studies of propofol. This was because patients in our study conformed to a tightly defined range in terms of age and degree of obesity; a deterioration in fit would be expected when using the model in a more general patient population.

Although the mean performance of the model was satisfactory, inter-individual variability was wide in all measures of performance. The most important measure of performance of the system is MDAPE, this was as large as 69% during the infusion phase. Our revised model did not perform any better in terms of MDAPE, indicating that other factors not assessed in an algorithm based solely on body weight were responsible for the between-patient variability. The relatively small degree of wobble and divergence indicates that the system was better at maintaining a constant blood concentration than at predicting what that concentration would be. So long as the target concentration was adjusted according to clinical response, the system performed well in clinical practice.

There was a decrease in accuracy during the recovery phase, but this is not of major clinical relevance compared with the ability of the algorithm to maintain a stable blood concentration during the infusion phase. However, it does indicate that an alternative model may describe the recovery phase better. More blood sampling during the recovery period would be required to develop such a model than was performed during the current study.

In summary, we have found a system for propofol infusion described originally by White and Kenny to perform adequately in a healthy adult Oriental patient population. However, wide inter-individual pharmacokinetic variability meant the system did not always perform well in individuals. The model described the infusion phase of anaesthesia more accurately than the recovery phase.

Acknowledgement

This study was supported by a Hong Kong Universities and Polytechnics Grants Committee direct grant for research, No. 220402970.

References

1. Short TG, Aun CST, Tan P, Wong J, Tam YH, Oh TE. A prospective evaluation of pharmacokinetic model controlled infusion of propofol in paediatric patients. *British Journal of Anaesthesia* 1994; 72: 302–306.
2. Marsh B, White M, Morton N, Kenny GNC. Pharmacokinetic model driven infusion of propofol in children. *British Journal of Anaesthesia* 1991; 67: 41–48.
3. White M, Kenny GNC. Intravenous propofol anaesthesia using a computerised infusion system. *Anaesthesia* 1990; 45: 204–209.
4. Gepts E, Camu F, Cockshott ID, Douglas EJ. Disposition of propofol administered as constant rate intravenous infusions in humans. *Anesthesia and Analgesia* 1987; 66: 1256–1263.
5. Varvel JR, Donoho DL, Shafer SL. Measuring the predictive performance of computer-controlled infusion pumps. *Journal of Pharmacokinetics and Biopharmaceutics* 1992; 20: 63–94.
6. Kataria BK, Ved SA, Nicodemus HF, Hoy GR, Lea D, Dubois MY, Mandema JW, Shafer SL. The pharmacokinetics of propofol in children using three different data analysis approaches. *Anesthesiology* 1994; 80: 104–122.

British Journal of Anaesthesia 1996; **76**: 316–318

Effect of ondansetron on nausea and vomiting after middle ear surgery during general anaesthesia

P. HONKAVAARA

Summary

The efficacy of ondansetron 4 mg and 8 mg was compared with placebo in the reduction of postoperative nausea, retching and vomiting (PONV) after middle ear surgery during general anaesthesia, in 75 patients, in a double-blind and randomized study. Both doses of ondansetron were predictors for a decrease in PONV and the number of doses of rescue antiemetic needed per patient (droperidol: from 0.72 in the placebo group to 0.32 in both the 4-mg and 8-mg groups). No reduction in PONV was observed in patients with a history of motion sickness, whereas in patients without a history of motion sickness, ondansetron reduced both the proportion of patients suffering from PONV from 53% to 20% ($P < 0.05$) and of those needing droperidol from 53% to 17% ($P < 0.05$). (*Br. J. Anaesth.* 1996; **76**: 316–318)

Key words

Vomiting, nausea. Vomiting, antiemetics. Surgery, otolaryngological.

In two recent studies, 62% and 80% of patients in placebo groups developed postoperative nausea and vomiting (PONV) after middle ear operations [1, 2]. Ondansetron has been found to be effective in preventing and treating PONV after general anaesthesia, and its safety profile is good with the recommended doses of 4 and 8 mg. Ondansetron is said to have a significant antiemetic effect on patients suffering from opioid-induced emesis. Middle ear surgery may disturb the vestibular system, and opioids increase vestibular sensitivity. On the other hand, vestibular stimulation increases the incidence of nausea and vomiting caused by opioids. The site of inhibitory action of ondansetron on PONV after middle ear surgery might be the nucleus tractus solitarius which has a high concentration of 5-HT_3 receptors.

The use of prophylactic ondansetron on PONV after middle ear operations has not been studied previously and the present study was designed to examine this area.

Methods and results

The Ethics Committee of the Otolaryngological Hospital approved the study, and informed consent was obtained from 75 patients undergoing middle ear surgery. All were ASA I–II, aged 15–62 yr. Exclusion criteria included: regular or temporary use of antiemetic drugs, and vomiting or retching within 24 h before operation. Twenty-five patients were allocated randomly to one of three groups; placebo, ondansetron 4 mg or ondansetron 8 mg. The design of the study was double-blind. On the preceding day, a history of motion sickness and PONV, and menstrual date were obtained.

A standard anaesthetic technique was used. Premedication comprised oxycodone 0.1 mg kg^{-1} and atropine 0.01 mg kg^{-1}. After insertion of an i.v. cannula, patients received the test drug in 5–7 min (ondansetron 4 mg or 8 mg (Zofran) or placebo diluted to 100 ml in 0.9% NaCl) in a double-blind manner. Anaesthesia was induced with thiopentone 5 mg kg^{-1}, preceded by fentanyl 2 μg kg^{-1}, which was given thereafter during surgery as 50-μg doses. Alcuronium 2–2.5 mg was used for "precurarization" and tracheal intubation was facilitated with suxamethonium 1.5 mg kg^{-1}. Anaesthesia was maintained with isoflurane (inspiratory concentration 0.5–1.5 vol%, mainly 0.75 vol%) and 66% nitrous oxide (which was replaced by air before closing of the tympanic membrane) in oxygen. Arterial pressure and heart rate were maintained within 20% of preanaesthetic values. End-tidal carbon dioxide concentration was kept at 5.0–5.5%. Vecuronium was used for neuromuscular block and residual block was antagonized with neostigmine 2 mg and glycopyrronium 0.4 mg. Arterial pressure, capnogram, electrocardiogram, haemoglobin oxygen saturation (Sp_{O_2}) and neuromuscular block were monitored routinely.

Postoperative pain was treated with diclofenac 1 mg kg^{-1} twice daily or paracetamol 10 mg kg^{-1} four times daily in patients who did not tolerate diclofenac. In addition, oxycodone 50 μg kg^{-1} i.v. or 100 μg kg^{-1} i.m. was used if needed for additional analgesia.

A trained nurse, who was unaware of the nature of the study drug, assessed the incidence of nausea, retching and vomiting at the following times: 0–2, 2–6, 6–12, 12–18 and 18–24 h after the end of anaesthesia. Droperidol 10 μg kg^{-1} i.v. or i.m. was given for vomiting, retching or prolonged nausea, at a minimum interval of 30 min.

PEKKA HONKAVAARA, MD, Department of Anaesthesia, Otolaryngological Hospital, University of Helsinki, Haartmaninkatu 4E, FIN-00290 Helsinki, Finland. Accepted for publication: October 2, 1995.

Table 1 Effect of ondansetron (4 mg and 8 mg) after middle ear surgery in patients without a history of motion sickness on PONV and the need for rescue antiemetics (number of patients). $*P < 0.05$ (Fisher's exact test), $**P < 0.01$ (Mann–Whitney U)

	Placebo	Ondansetron
Patients (n)	19	30
Sex (M/F)	11/8	18/12
Ondansetron 0/4 mg/8 mg	19/0/0	0/16/14
Patients free of PONV (%)	47	80*
Patients suffering from retching or vomiting (%)	37	10*
Patients needings droperidol (%)	53	17*
Doses of droperidol needed per patient (median (range))	1 (0–3)	0 (0–2)**

Patients in the placebo and ondansetron groups did not differ significantly in age, weight, sex, phases of the menstrual cycle, details of anaesthesia, duration of anaesthesia or operation, mean concentration of inspired isoflurane, total dose of fentanyl given, dose of lignocaine given topically during surgery or need for oxycodone after operation. There were no side effects from the test drug in any of the groups.

After surgery, 12 %, 12 % and 24 % of the patients in the placebo group suffered from nausea, retching and vomiting, respectively. The corresponding values in the ondansetron 4 mg group were 16 %, 4 % and 8 %, and in the 8 mg group, 4 %, 16 % and 16 %.

In the search for factors associated with PONV, logistic regression analysis revealed that ondansetron, both 4 mg ($P < 0.05$) and 8 mg ($P < 0.05$), a history of motion sickness ($P < 0.05$) and female sex ($P < 0.01$) were predictors of PONV and the need for rescue antiemetic, but the amount of oxycodone was not a predictor of these effects.

Twelve patients in the placebo group needed droperidol, but only six and seven patients in the ondansetron 4 and 8 mg groups, respectively. The need for rescue antiemetic, in mean doses per patient, was 0.72 (0.89) in the placebo group, 0.32 (0.63) in the ondansetron 4 mg and 0.32 (0.56) in the ondansetron 8 mg group.

In the 49 patients *without a history of motion sickness*, prophylaxis with ondansetron 4 mg and 8 mg decreased both the proportion of patients suffering from PONV and the need for droperidol (table 1).

Comment

The main finding in this study was that prophylaxis with ondansetron reduced PONV and the need for droperidol. There was a marked reduction in the number of patients suffering from PONV and also the need for droperidol in those without a history of motion sickness.

The overall percentage of placebo-treated patients reporting emetic symptoms in this study was in agreement with two recent studies on PONV after middle ear surgery under general anaesthesia [1, 2].

The mechanism of PONV after ear operation is still obscure. Increased middle ear pressure caused by nitrous oxide has been postulated as one of the mechanisms. This was unlikely in the present study as nitrous oxide was replaced by air well before closing of the tympanic membrane and thus no pressure was generated in the middle ear from diffusion of nitrous oxide.

One of the causes of PONV after middle ear surgery could be the physical stimulus caused by the otologist drilling and irrigating the bone adjacent to the inner ear. High levels of noise caused by drilling and suctioning have been reported in ear surgery, and noise exceeding 107 dB(A) has been measured in the mastoid cavity [3]. The otologist also causes low frequency vibrations, especially when using a slowly rotating cutting burr. These vibrations may act in the same way as infrasound on the vestibular system. It has been shown that low-frequency sound stimulation provokes postural instability in patients undergoing surgery for chronic otitis media [4].

This action of noise is termed the Tullio phenomenon, and is caused by loud sound waves activating the vestibular part of the inner ear [4]. The postulate that physical stimulation is one of the causes of a high incidence of PONV after middle ear surgery is supported by the fact that transdermal hyoscine, a drug used in motion sickness, is more potent in reducing PONV [1, 2] than ondansetron, which lacks an anti-motion sickness effect [5].

Zacopride, another 5-HT$_3$ antagonist, overcomes the cognitive impairment which occurs with hyoscine [6]. Thus the combination therapy of transdermal hyoscine and a 5-HT$_3$-antagonist should cover patients with and without motion sickness and may lead to less PONV with lesser side effects, but this hypothesis requires evaluation before it can be recommended.

We conclude that the use of prophylactic ondansetron reduced PONV and the need for antiemetics after surgery of the middle ear under general anaesthesia. Patients without a history of motion sickness benefited more from this prophylaxis. We recommend a dose of 4 mg, as increasing the dose to 8 mg did not decrease PONV or the need for rescue antiemetic.

References

1. Reinhart DJ, Klein KW, Schroff E. Transdermal scopolamine for the reduction of postoperative nausea in outpatient ear surgery: a double-blind, randomized study. *Anesthesia and Analgesia* 1994; **79**: 281–284.
2. Honkavaara P, Saarnivaara L, Klemola U-M. Prevention of nausea and vomiting with transdermal hyoscine in adults after middle ear surgery during general anaesthesia. *British Journal of Anaesthesia* 1994; **73**: 763–766.
3. Parkin LP, Wood GS, Wood RD, McCandless GA. Drill and suction-generated noise in mastoid surgery. *Archives of Otolaryngology* 1980; **106**: 92–96.
4. Ishizaki H, Pyykkö I, Aalto H, Starck J. Tullio phenomenon and postural stability: Experimental study in normal subjects and patients with vertigo. *Annals of Otology, Rhinology and Laryngology* 1991; **100**: 976–983.
5. Stott JRR, Barnes GR, Wright RJ, Ruddock CJS. The effect on motion sickness and oculomotor function of GE 38032F, a 5-HT$_3$-receptor antagonist with antiemetic properties. *British Journal of Clinical Pharmacology* 1989; **27**: 147–157.

British Journal of Anaesthesia 1996; **76**: 319–321

Extradural analgesia with clonidine and fentanyl compared with 0.25% bupivacaine in the first stage of labour

D. J. BUGGY AND C. MACDOWELL

Summary

Conventional extradural analgesia during labour with 0.25–0.375% bupivacaine may induce motor weakness and subjective sensory deficit, reducing maternal satisfaction. Even in a regimen for ambulatory extradural analgesia (0.1% bupivacaine–fentanyl 2 μg ml^{-1}), a potential for proprioreception impairment exists, which may impair safe ambulation. We have combined fentanyl with clonidine for extradural analgesia in labour, and compared its effects with 0.25% bupivacaine, in a randomized, double-blind study. We studied 28 women requesting extradural analgesia for labour; they were allocated randomly to either group 1, who received clonidine 120 μg with fentanyl 50 μg, or group 2, who received bupivacaine 25 mg. Detailed clinical neurological examination was undertaken 30 min later. Pain was assessed subjectively using a 10-cm visual analogue scale (VAS). There were no significant differences in VAS between the groups at any time. Median onset of analgesia was longer in group 1 (24.3 (interquartile range 20–35) compared with 17.5 (15–25) min) ($P < 0.05$) and 79% of group 1 *vs* 86% of group 2 patients reported a high degree of satisfaction with extradural analgesia. Patients in group 2 had a much higher incidence of motor weakness ($P < 0.01$), impaired perception of pinprick ($P < 0.01$) and impaired distal joint proprioception ($P < 0.05$) than group 1. We conclude that clonidine 120 μg–fentanyl 50 μg provided comparable extradural analgesic efficacy as 0.25% bupivacaine for the first stage of labour. Furthermore, unwanted neurological effects were significantly less. (*Br. J. Anaesth.* 1996; **76**: 319–321)

Key words

Anaesthetics local, bupivacaine. Anaesthetic techniques, extradural. Analgesics opioid, fentanyl. Analgesia, obstetric. Sympathetic nervous system, clonidine.

Local anaesthetics, most commonly bupivacaine, administered repeatedly for extradural analgesia in labour may cause progressive motor block even if relatively dilute concentrations are used. This has resulted in decreased maternal satisfaction with extradural analgesia [1]. The introduction of ambulatory extradural analgesia, using very dilute concentrations of local anaesthetics, in combination with adjuvants such as fentanyl and adrenaline, has allowed greater mobility and maintenance of near normal somatic sensation [2]. However, clinical impairment of distal joint proprioception after an ambulatory extradural regimen has been reported recently, giving rise to anxiety that safe ambulation may be impaired even in the presence of apparently normal lower limb motor function [3]. Clonidine, in common with opioids, has successfully enhanced bupivacaine-induced extradural analgesia in labour [4], but its use alone for postoperative extradural analgesia has been disappointing. Clinical trials of extradural opioids alone have yielded conflicting results [5]. However, intrathecal opioids, used alone or as part of a combined spinal–extradural technique, seem promising [5].

No prevous study has assessed the impact of combining fentanyl with clonidine, without local anaesthetic, to provide extradural analgesia for the first stage of labour. We hypothesized that unwanted neurological effects should be greatly diminished with this combination. The purpose of this study, therefore, was to compare the analgesic efficacy and effect on proprioception and motor weakness of combining these two analgesic adjuvants, with 0.25% bupivacaine, for extradural analgesia in labour.

Methods and results

After obtaining informed consent and local Ethics Committee approval, we studied 32 women ($n = 22$ nullipara) in established labour (minimum 3 cm cervical dilatation, 80% cervical effacement). Patients with more than 6 cm cervical dilatation, intercurrent disease or those with a complicated pregnancy were excluded. No patient had received any analgesia before the extradural.

After administration of Hartmann's solution 500 ml i.v. to the patient, an extradural cathether was sited at the L2–3 or L3–4 intervertebral space. Patients were allocated randomly to one of two groups, and extradural analgesia was administered in a double-blind design, that is the anaesthetist,

---

DONAL J. BUGGY*, MSC, MRCPI, DME, FFARCSI, CARLOS MACDOWELL, FFARCSI, FRCA, Department of Anaesthesia, International Missionary Training Hospital, Drogheda, County Louth, Ireland. Accepted for publication: September 21, 1995.

*Address for correspondence: Department of Anaesthesia, Beaumont Hospital, Dublin 9, Ireland.

midwives and patients were unaware of which analgesic regimen was being used. The hospital pharmacist prepared the study solutions in coded 10-ml syringes, and arranged randomization according to computer-generated random numbers. Patients in group 1 received clonidine 120 µg (0.8-ml solution) and fentanyl 50 µg (1-ml solution), made up to 10 ml with normal saline. These doses were chosen because previous studies on postoperative patients found them to be safe and effective [2, 4, 6]. Patients in group 2 received bupivacaine 25 mg in a 10-ml solution. No test dose was given. If patients were receiving an oxytocin infusion, it was stopped during insertion of the extradural and until analgesia to half the baseline visual analogue scale (VAS) score was achieved. Non-invasive arterial pressure and continuous fetal heart monitoring were maintained in all patients during labour.

Subjective perception of maximum pain intensity during uterine contraction was recorded on a 10-cm VAS before insertion of the extradural cathether and at 5-min intervals thereafter for the first 40 min, and then at 60- and 90-min intervals. The time taken for the baseline VAS to be reduced by 50 % was noted retrospectively. Subsequent analgesia was provided by an extradural infusion of 0.1 % bupivacaine, prepared by the anaesthetist and commenced by the midwife at a rate of 3–6 ml h^{-1}, at her discretion, if VAS scores increased to > 4 or if patient discomfort increased. The time from the initial bolus to commencement of this infusion was noted as the duration of analgesia. After delivery, overall satisfaction with extradural analgesia was recorded by the patient on a four-point scale: excellent, good, fair or poor. If analgesia was inadequate, a 5-ml bolus of 0.25 % bupivacaine was given.

Thirty minutes after the initial bolus, a detailed, clinical neurological examination of the lower trunk and limbs was performed by the same observer, as described previously [3]. Maternal arterial pressure (standing and recumbent), and any pruritus or shivering, and sedation levels were also recorded. Sedation was graded on a four-point scale: awake, drowsy, dozing (eyes shut intermittently) or asleep (but rousable on being spoken to). Hypotension was defined as a decrease in systolic arterial pressure of at least 30 %, and was treated by giving another 250 ml of Hartmann's solution i.v., repeated as necessary. Fetal heart rate was noted throughout labour using a cardiotocograph. After delivery, neonatal Apgar scores were recorded at 1 and 5 min.

The groups were similar in physical and labour characteristics. Four patients were subsequently lost from the study ($n = 3$ multiparae) because delivery occurred within 60 min of extradural catheter insertion. There was a comparable degree of analgesia, as assessed by VAS, between the two groups at all times. Median onset of analgesia (defined as the time taken for the baseline VAS to be reduced by 50 %) was significantly longer in group 1 (24.3 (interquartile range 20–35) *vs* 17.5 (15–25) min) ($P < 0.05$). When established, however, duration of analgesia provided by both regimens was similar. Median consumption of 0.1 % bupivacaine infusion was similar in each group. Eleven (79 %) patients in group 1 and 12 (86 %) in group 2 recorded an "excellent or good" overall satisfaction rating for their analgesia (table 1).

Table 1 Labour, analgesia and neurological characteristics in the two groups. $^{*}P < 0.05$, $^{**}P < 0.01$

	Clonidine/ fentanyl ($n = 14$)	0.25 % Bupivacaine ($n = 14$)
Age (yr) (mean (range))	24.4 (15–36)	27.0 (21–43)
Weight (kg) (mean (SD))	73.1 (2.3)	74.8 (1.9)
Oxytocin (*n* (%))	4 (29 %)	8 (57 %)
Cervical dilatation (cm) (mean (interquartile range))	3.5 (3.0–4.5)	3.6 (3.0–4.5)
Primigravida (*n* (%))	11 (77 %)	10 (71 %)
Duration of labour (h) (median (interquartile range))	6.4 (5.0–8.25)	6.9 (5.5–9.0)
Onset (min) (median (interquartile range))	24.3 (20–35)	17.5 (15–25)
Duration of analgesia (min) (mean (SD))	80.0 (60–90)	77.1 (55–90)
0.1 % Bupivacaine infused (ml) (median (interquartile range))	32 (24–44)	35 (28–45)
Apgar score (median (interquartile range))		
1 min	7.25 (5.75–10)	7.5 (6.25–10)
5 min	9.25 (8–10)	9.0 (8–10)
Satisfaction (*n* (%))	11 (79 %)	12 (86 %)
Muscle power (MRC grade < 3) (*n*)	1	8**
Impaired proprioception (*n*)	4	10*
Impaired vibration sense (*n*)	2	4
Romberg's sign (+) (*n*)	2	6
Impaired pinprick perception (T10–L4)	0	7**
Hypotension (*n*)	8 (57 %)	4 (29 %)

Patients in group 2 had significantly more motor weakness and impaired perception of pinprick, characterized by anaesthesia (no sensation) or analgesia (sharp stimulus perceived as blunt). All patients in group 1 had preserved spinothalamic-mediated sensation (pinprick and temperature), in spite of reporting significant analgesia for labour pain. The incidence of impaired proprioception was also significantly higher in group 2, but differences in the other posterior column sensory modalities were not significant (table 1). Median sensory level was T10 in both groups.

There were no significant differences between groups in lowest systolic pressure, or the incidences of commonly reported side effects of the drugs used. Eight of 14 patients in the clonidine–fentanyl group had hypotension compared with four of 14 in the bupivacaine group. However, because of the low overall incidence of side effects, together with the low numbers studied, the power of this study to detect true differences in these side effects was only 30 % for sedation and 45 % for hypotension.

Comment

We chose to compare a clonidine–fentanyl regimen with 0.25 % bupivacaine, rather than an ambulatory regimen of 0.1 % bupivacaine, because we found that the latter has suboptimal, short-lived analgesia when not combined with spinal anaesthesia [3]. In addition, favourable comparison with the analgesic efficacy of the higher dose of bupivacaine would be desirable with a new regimen. We did not allow our patients to walk as we were unaware which solution was used, and felt that 0.25 % bupivacaine would be unsafe.

Our data suggest that the side effect profile was low, with 11 patients unaffected by sedation; the remaining three patients showed only mild degrees of sedation. This contrasts with other studies of patients in labour using bupivacaine and clonidine, in which 50 % of patients had sedation scores of 2 or more [4]. Although hypotension occurred at some time during the study, it was twice as common in patients receiving the clonidine–fentanyl mixture, no patient reported symptoms attributable to it and no patient had postural hypotension. In our study, the degree of sedation and hypotension was mild. Pruritus was not a feature in our study. In common with other reports using these agents extradurally [2], our median neonatal Apgar scores were very satisfactory (table 1).

The occurrence in our bupivacaine-free group of a degree of posterior column impairment, together with the absence of segmental sensory changes, despite satisfactory analgesia for labour, is intriguing. Extradural clonidine prolongs the sensory and motor block induced by bupivacaine [4], but it is not known if it has intrinsic inhibitory effects on axonal transmission. Fentanyl, and surprisingly, normal saline administered extradurally, cause segmental sensory deficit, but again the mechanism is unclear [2].

A study of the neurological status of the lower limbs of women in labour receiving extradural analgesia with 0.1 % bupivacaine and fentanyl 2 $\mu g\ ml^{-1}$ was conducted in 50 primigravidae, and there was a high incidence of posterior column sensory impairment [3]. Although the present study did not directly compare them, it may be safer for patients receiving clonidine–fentanyl to walk than a group receiving an ambulatory regimen (e.g. 0.1 % bupivacaine with fentanyl 2 $\mu g\ ml^{-1}$), because of decreased unwanted neurological impairment. Moreover, a comparison of extradural fentanyl alone with 0.04 % bupivacaine, adrenaline 1.7 $\mu g\ ml^{-1}$ and fentanyl 1.7 $\mu g\ ml^{-1}$ (BAF) found that 70 % of patients receiving each regimen could walk, but motor weakness and orthostatic hypotension occurred in significantly more patients in the BAF group [6]. We acknowledge, however, that experience of more than 7000 cases of ambulatory extradural analgesia recorded no incidence of falling. Such large series of safe reports on the use of the ambulatory regimen of extradural analgesia suggest that the theoretical risk of falling from impaired posterior column sensation is minimal. In addition, our patient numbers were small, and larger studies are required to confirm the safety of the clonidine–fentanyl regimen in terms of its potential side effects.

Acknowledgement

We thank our Chief Hospital Pharmacist, Ms Caitriona Craven and Drs Gillian O'Kane and Niall Hughes, Consultant Anaesthetists.

References

1. Murphy JD, Hutchinson K, Bowden MI, Lewis M, Cooper GM. Bupivacaine versus bupivacaine plus fentanyl for epidural analgesia: effect on maternal satisfaction. *British Medical Journal* 1991; **302**: 564–567.
2. Hore PJ, Silbert BS, Cook RJ, Beilby DS. A double-blind assessment of segmental sensory changes with epidural fentanyl versus epidural saline in patients undergoing extracorporeal shock-wave lithotripsy. *Anesthesiology* 1990; **72**: 603–606.
3. Buggy D, Hughes N, Gardiner J. Posterior column sensory impairment during ambulatory extradural analgesia in labour. *British Journal of Anaesthesia* 1994; **73**: 540–542.
4. O'Meara ME, Gin T. Comparison of 0.125 % bupivacaine with 0.125 % bupivacaine and clonidine as extradural analgesia in the first stage of labour. *British Journal of Anaesthesia* 1993; **71**: 651–656.
5. Morgan M. The rational use of intrathecal and extradural opioids. *British Journal of Anaesthesia* 1989; **63**: 165–188.
6. Breen TW, Shapiro T, Glass B, Foster-Payne D, Oriol NE. Epidural anesthesia for labor in an ambulatory patient. *Anesthesia and Analgesia* 1993; **77**: 919–924.

British Journal of Anaesthesia 1996; **76**: 322–324

CASE REPORTS

Sudden onset of subarachnoid block after subdural catheterization: a case of arachnoid rupture?

D. W. Elliott, F. Voyvodic and P. Brownridge

Summary

We describe a patient who received an apparently uneventful extradural block in labour but developed rapid extension of neural block within minutes of receiving her first incremental dose 2 h later. Computed contrast tomography revealed radio-opaque dye within both the subdural and sub-arachnoid spaces, but none within the extradural space. This case report demonstrates that subdural spread of low-dose local anaesthetics is not always clinically distinguishable from extradural analgesia and that the arachnoid membrane may subsequently perforate with potentially serious consequences. (*Br. J. Anaesth* 1996; **76**: 322–324)

Key words

Anaesthesia, obstetric. Anaesthetic techniques, extradural. Complications, subarachnoid block.

Case report

A 23-yr-old nulliparous Asian woman requested extradural analgesia for pain relief in early labour. The patient was in good health and there were no contraindications to the procedure. She was of slim build and her spine was easily palpable. The operator (D.W.E.) had previously performed approximately 50 extradurals without complication. With the patient in a sitting position, an 18-gauge Tuohy needle was inserted into the extradural space at the L3–4 interspace without difficulty. Loss of resistance to air was detected at 4 cm and an extradural catheter (Portex, Kent) was inserted with minimal resistance. After removal of the Tuohy needle, however, it was estimated that no more than 1 cm of catheter was lying within the extradural space. Consequently, the procedure was repeated using the same interspace and a new catheter inserted without difficulty such that an estimated total of 4 cm lay within the extradural space. The extradural needle was not rotated on either attempt and the patient did not complain of pain, paraesthesia or headache during insertion of the catheter. Nothing could be aspirated from the needle or catheter on either occasion.

After a further negative aspiration test with the patient lying on her side, a 3-ml dose of 0.25% bupivacaine was given via the catheter. This test dose produced no detectable sensory or motor changes and after 5 min another 7 ml of the same solution were given. Satisfactory analgesia was achieved approximately 5 min later and there was no change in arterial pressure. When so instructed, the patient was able to raise both legs from the surface of her bed. No further formal assessment of the height of the block was made.

Two hours later, further analgesia was requested. With the patient in a semi-recumbent position, and after a negative aspiration test, a pre-mixed proprietary preparation containing bupivacaine 12.5 mg and pethidine 25.0 mg in saline 10 ml (Delta West, Perth, Australia) was injected by the attending midwife via the extradural catheter. Five minutes later, the patient complained of nausea, shortness of breath and numbness in her hands and face. An urgent request by the midwife for an anaesthetic review was met within minutes.

On examination, the patient was found to be drowsy but responsive to questions and commands. She was unable to move either of her lower limbs but retained a weak bilateral handgrip and was still able to lift her head from the pillow. Anaesthesia to cold was present over the entire chest wall below the clavicles but there was no sensory loss over the face and neck. Marked nystagmus was observed. The pupils were small and equal, and it is possible that bilateral ptosis was present, although it was difficult to be certain because of the patient's ethnic origin and her state of drowsiness. There was no obvious injection of the sclerae and both nostrils were patent, but the presence of a bilateral Horner's syndrome could not be excluded.

During this period of assessment, the patient remained remarkably calm and co-operative. Her arterial pressure did not change and there were no signs of respiratory depression or fetal distress. Despite complaining of some shortness of breath, her vital capacity was recorded as 1.5 litre. She was given supplementary oxygen and pulse oximetry revealed an oxygen saturation of 99%. In view of these findings, it was decided not to administer naloxone unless there was any deterioration in her state of consciousness or ventilation.

A provisional diagnosis of subarachnoid catheter migration was made and instructions given that further analgesia would be administered only by an anaesthetist. Over the next 2 h there was complete recovery of neural function. Five further top-up doses consisting of 0.25% bupivacaine 2 ml were

---

D. W. Elliott, mb, bs, P. Brownridge, frca, fanzca (Department of Anaesthesia and Intensive Care); F. Voyvodic, mb, bs, (hons), dracr (Department of Radiology); Flinders Medical Centre, Bedford Park, South Australia 5042. Accepted for publication: September 5, 1995.

Correspondence to P.B.

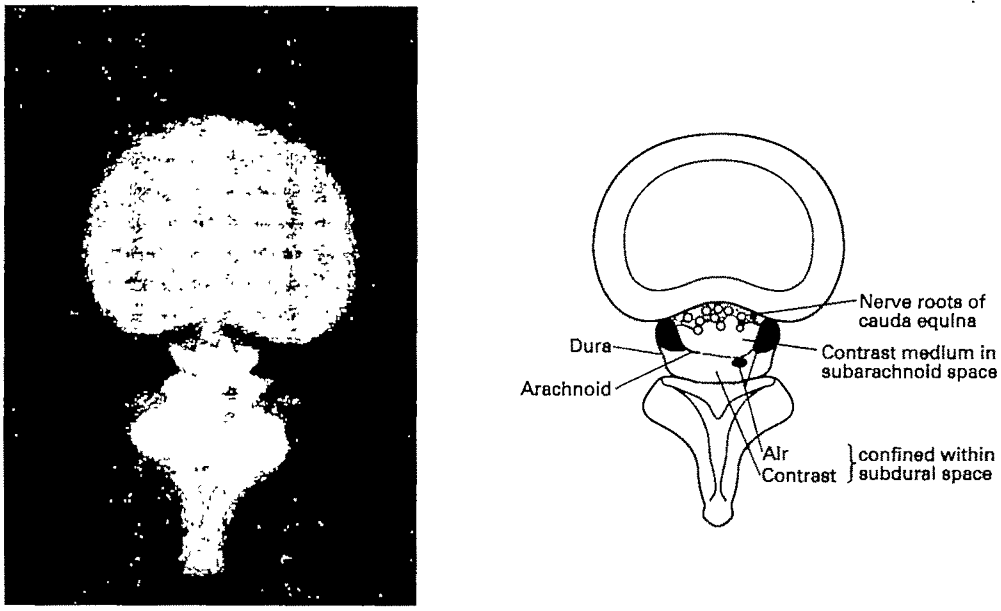

Nerve roots of cauda equina
Dura
Contrast medium in subarachnoid space
Arachnoid
Air
Contrast
confined within subdural space

Figure 1 Left: CT scan at L1–2. Contrast medium is layered posteriorly in the subarachnoid space with the cauda equina nerve roots clearly identified anteriorly. A further collection of contrast medium and air distends the subdural space. The extradural space is free of contrast medium. Right: diagrammatic representation of the CT.

given for pain during the rest of her labour. On each occasion, analgesia occurred within the duration of a contraction and lasted for an interval of 45–60 min. Incomplete motor block of the lower limbs returned after each injection. Eight hours after insertion of the extradural catheter, a healthy baby was delivered with the aid of outlet forceps.

Although we strongly suspected on clinical grounds that the catheter tip had ultimately become situated within the subarachnoid space, we were puzzled why the response to the initial dose had been so uneventful. In which compartment(s) had the catheter been originally placed? Did the catheter migrate from the extradural or subdural space, or was it in the subarachnoid space from the outset? To try and answer these questions we felt it would be useful to confirm the position of the catheter radiologically. The patient agreed to this proposal and gave her informed consent for computer tomography (CT) using contrast medium.

Four hours after delivery the patient was transferred to the CT scanner and 3 ml of iodinated contrast medium (iopamidol 300 mg ml^{-1}) were introduced via the extradural catheter; 5-mm thick contiguous axial CT scans were then performed through the upper lumber spine. This showed contrast medium only within the subdural and subarachnoid spaces while the extradural space was entirely contrast-free (fig. 1).

The day after delivery, the patient developed typical features of a dural puncture headache which gradually became more severe. An extradural blood patch was performed on day 4 and her headache disappeared after 3 h. She remained headache-free when discharged from hospital 2 days later.

Discussion

Subdural catheterization is a well recognized complication of extradural analgesia with an estimated incidence, according to one retrospective study, of 0.8% [1]. The diagnosis in that study, however, was based solely on clinical criteria and was not confirmed radiologically. The true incidence of subdural catheterization, therefore, remains unknown because a definitive diagnosis depends on CT imaging, an investigation that is justified only if catheter misplacement has been suspected clinically.

While two attempts were made to site the extradural catheter in our patient, the procedure was straightforward on both occasions; the first catheter was pulled out accidentally when the needle was removed. There was certainly no reason to believe that the dura had been perforated, injured or otherwise predisposed to catheter misplacement on either occasion, although such events can never be entirely excluded.

It has been claimed by various authors that subdural local anaesthetic spread can be diagnosed, or at least strongly suspected, on clinical grounds. According to Collier [2] for example, subdural spread is typically accompanied by: relatively slow onset of neural block (i.e. 15–20 min with further progression over the next 20 min); limited motor block; only moderate hypotension; progressive respiratory depression and inco-ordination rather than sudden apnoea; and recovery after 2 h [2]. Other clinical clues have also been suggested, such as: exaggerated hypotension and unexpectedly high motor block [1, 3, 4]; relative sparing of motor function in the lower limbs [4]; unilateral block [5]; the presence of a Horner's syndrome [3]; and, possibly, acute headache during injection [6]. Without radiological confirmation, however, the reliability of these clinical signs in distinguishing between extradural, subdural and subarachnoid injection is conjectural.

One of the important features in this case report is that our patient displayed none of the above symptoms or signs after the initial therapeutic dose.

Aspiration of both needle and catheter was negative, and there was no abnormal response to the test dose. Thus there were no grounds to believe that the catheter was other than correctly sited in the extradural space. Yet the CT scan clearly demonstrated no spread within the extradural space. This finding implies, therefore, that subdural spread of local anaesthetic drugs when given in *low* dosage is not necessarily clinically distinguishable from extradural or even subarachnoid spread.

In a previous case report, we described an obstetric patient in whom an extradural catheter was subsequently shown to have been confined solely within the subdural space [6]. We now report a patient in whom we believe the catheter was initially within the subdural space but later became situated intrathecally, as postulated in the review by Reynolds and Speedy [7]. While it has been found to be impossible to puncture the intact postmortem dura with a Portex catheter, the thinner arachnoid membrane is easily perforated [8]. Thus it is not difficult to appreciate how readily transarachnoid migration of a subdural catheter might occur in clinical practice.

In our patient, the clinical response to subsequent doses was so distinct from that following the initial dose that we felt confident in assuming that the catheter had become situated intrathecally. This was confirmed not only radiologically but also by the fact that she later developed a spinal headache. An alternative explanation might be that the side holes of the extradural catheter were situated within both the subdural and subarachnoid spaces from the outset and that any disparity in clinical response depended entirely on the vagaries of differential flow [9, 10]. However, the fact that our patient responded so consistently to subsequent doses, and that the extradural space was altogether free of radio-opaque dye makes this alternative explanation, we believe, exceedingly unlikely.

Fortunately, the initial intrathecal dose was not sufficient to cause severe respiratory or circulatory depression in our patient and resuscitation was not required. This is now the second time a mixture of bupivacaine 12.5 mg and pethidine 25 mg has been given intrathecally in our unit without causing serious harm or injury [11]. Our experience thus supports the contention that extradural management during labour is associated with an intrinsically greater margin of safety when local anaesthetics are used in low doses [12].

If our interpretation of events concerning this case report is correct, then presumably a subdural catheter can perforate the arachnoid membrane and become situated within the subarachnoid space at any time. This, too, has important implications. Although our patient received intermittent bolus doses, there is no reason to believe that other regimens, such as continuous infusions or patient-controlled extradural analgesia, are immune to transarachnoid migration. Our case report helps to explain just how easily subdural catheter placement may escape notice, and reinforces the need to meet recommended standards of supervision and management among all patients receiving extradural analgesia in labour, irrespective of the drug delivery system.

References

1. Lubenov T, Keh-Wong E, Kristof K, Ivankovich O, Ivankovich AD. Inadvertent subdural injection: a complication of an epidural block. *Anesthesia and Analgesia* 1988; **67**: 175–179.
2. Collier C. Total spinal or massive subdural block? *Anaesthesia and Intensive Care* 1982; **10**: 92–93.
3. Lee A, Dodd KW. Accidental subdural catheterisation. *Anaesthesia* 1986; **41**: 847–849.
4. Lowenwirt I, Citron A, Krishnamurthy U. Successful subdural anesthesia for cesarean section and postoperative pain management. *International Journal of Obstetric Anesthesia* 1995; **4**: 120–122.
5. Brindle Smith G, Barton FL, Watt JH. Extensive spread of local anaesthetic solution following subdural injection of an epidural catheter during labour. *Anaesthesia* 1984; **39**: 355–358.
6. McMenemin IM, Sissons GRJ, Brownridge P. Accidental subdural catheterization: Radiological evidence of a possible mechanism for spinal cord damage. *British Journal of Anaesthesia* 1992; **69**: 417–419.
7. Reynolds F, Speedy HM. The subdural space: the third space to go astray. *Anaesthesia* 1990; **45**: 120–123.
8. Hardy PAJ. Can epidural catheters penetrate dura mater. An anatomical study. *Anaesthesia* 1986; **41**: 1146–1147.
9. Ward CF, Osborne R, Benumof JL, Saidman LJ. A hazard of double-orifice epidural catheters. *Anesthesiology* 1978; **48**: 362–364.
10. Power I, Thorburn J. Differential flow from multihole epidural catheters. *Anaesthesia* 1988; **43**: 876–878.
11. Brownridge P. Another misplaced epidural catheter. *Anaesthesia and Intensive Care* 1984; **12**: 369–371.
12. Van Steenberge A. In: Doughty, A, ed. *Epidural Analgesia in Obstetrics*. London: Lloyd-Luke, 1980; 129–133.

British Journal of Anaesthesia 1996; **76**: 325–327

Elective forceps delivery and extradural anaesthesia in a primigravida with portal hypertension and oesophageal varices

J. A. Heriot, C. M. Steven and R. S. Sattin

Summary

The use of extradural analgesia to avoid straining in a primigravida with portal hypertension and secondary oesophageal varices is described, together with a discussion of the advantages and disadvantages of this approach. (*Br. J. Anaesth.* 1996; **76**: 325–327)

Key words

Anaesthetic techniques, extradural. Anaesthesia, obstetric. Complications, hypertension. Complications, oesophageal varices.

Case report

A 31-yr-old Caucasian primigravida presented for antenatal care at 11 weeks' gestation. Past medical history included a diagnosis of portal vein hypertension secondary to idiopathic portal vein thrombosis, having presented with haematemesis at 4 yr of age. She was found to have hepatosplenomegaly and, at 5 yr of age, a splenectomy was performed to treat thrombocytopenia. At booking, her arterial pressure was 120/70 mm Hg, weight 57.3 kg and height 1.7 m.

She suffered a small haematemesis at 8 weeks' gestation which was treated by admission and observation in hospital. Although her portal hypertension was regularly followed-up at a specialist teaching hospital, she wished to have her baby delivered locally. She was seen in the antenatal clinic by a consultant anaesthetist to discuss pain relief in labour. The patient said that she did not want to be immobilized by an extradural but understood that an elective forceps delivery was planned. Prophylactic endoscopic banding of her oesophageal varices, which were moderately large from the gastro-oesophageal junction to the mid-oesophagus, was performed uneventfully at 16, 25 and 31 weeks' gestation.

She was admitted to the labour ward in spontaneous labour at term plus 5 days. Vaginal examination demonstrated intact membranes, 4 cm cervical dilatation and a thinning cervix. The medical team and intensive care unit were informed of her admission and a Sengstaken–Blakemore tube was available. An i.v. infusion was commenced and blood obtained for investigation and cross-matching. Full blood count, clotting and liver function tests were normal. An extradural was sited at the L2–3 interspace, in the left lateral position, using a 16-gauge Tuohy needle with loss of resistance to saline. Analgesia was established using a solution of 0.1 % plain bupivacaine and fentanyl 2 μg ml^{-1}; 10 ml was given as the initial bolus with 10–15-ml supplementary doses.

The patient's membranes ruptured after 4 h of labour and an i.v. infusion of oxytocin was commenced after 8 h (the delay in these events was initial reluctance by our patient of any methods to augment labour). The extradural was maintained subsequently with increments of 0.25 % plain bupivacaine to prevent any desire to "bear down". The first stage lasted 12 h 36 min. The second stage lasted 41 min and a live male infant weighing 3.48 kg, with Apgar scores of 7 and 9, was delivered vaginally by elective use of Anderson forceps. A physiological third stage lasted 18 min, the placenta was healthy, complete and weighed 600 g. Uterine contraction was satisfactory and the decision was made not to administer the combination of ergometrine and syntocinon in order to avoid the risk of inducing hypertension and the autotransfusion effect of more aggressive uterine contraction. Total blood loss was 300 ml.

The puerperium was uneventful with no haematemesis or change in liver function.

Discussion

In a pregnant woman with known oesophageal varices, the decision to deliver the fetus by lower segment Caesarean section or vaginally is controversial. It is already known that pregnant women with extrahepatic portal vein obstruction have a fetal loss rate of one-third and a 400 times increased mortality rate [1]. However, although these cases are rare, these patients have normal fertility and usually normal liver function, and the main hazard is variceal haemorrhage, unlike those with chronic active hepatitis and portal hypertension who also risk developing acute hepatic failure.

As in our patient, variceal bleeding from extrahepatic pre-sinusoidal portal hypertension usually occurs first in childhood or adolescence and is the

---

J. A. Heriot*, MB, BS, FRCA, DRCOG, C. M. Steven, MB, ChB, FRCA, St Helier's Hospital, Wrythe Lane, Carshalton, Surrey SM5 1AA. R. S. Sattin†, MB, BS, MRCOG, St Richard's Hospital, Chichester PO19 4SE. Accepted for publication: September 8, 1995.

Present addresses:

* St George's Hospital, Blackshaw Road, London SW17 0RE.

† Lister Hospital, Corey's Mill Lane, Stevenage Herts SG1 4AB.

Correspondence to J. A. H.

commonest mode of presentation. The first haemorrhage often occurs at about 4 yr of age if the pathology has a neonatal origin such as umbilical or intra-abdominal infection, or septicaemia [2]. This group normally tolerates haemorrhage well as they tend to have good cardiovascular and hepatic reserve and cessation of bleeding occurs without intervention in up to 20 % of cases [3].

There is varied opinion on the risk of bleeding from varices during pregnancy itself. Blood volume in pregnancy increases by a maximum of 40–45 %. This volume is taken up partially by the splanchnic system and great veins, and increases right heart pressure, thereby increasing the portal venous pressure in the later stages of pregnancy. Transient oesophageal varices may develop in two-thirds of healthy pregnant women [4]. As the fetus grows, venous return is reduced via the inferior vena cava. Classic studies in 1963 and 1964 [5, 6] indicated that the inferior vena cava is normally occluded in the supine position in late pregnancy and that venous return occurs via the azygos and vertebral veins. Although this inferior vena cava occlusion is greatly relieved in the lateral position, collateral flow through the pathological varices is increased and so is the risk of their bleeding [7]. Another view is that from a comprehensive review by Britton [8], who concluded that fatal haemorrhage from pre-existing oesophageal varices is not more likely to occur during gestation and that it is not predictable on the basis of individual history of bleeding. When haemorrhage does occur it is usually in the second trimester and this may be linked to the maximum expansion in total blood volume at the end of the second trimester [8].

Various methods have been used to treat variceal haemorrhage, including the Sengstaken–Blakemore tube, shunt procedures, endoscopic sclerotherapy [9–11] and, more recently, banding. Our patient had a haematemesis at 8 weeks' gestation and it was decided to apply bands to the varices using endoscopy. This was performed three times and it was felt that the advantages of reducing the risk of life-threatening haemorrhage outweighed possible disadvantages. This patient had no further haematemeses during pregnancy or in the postpartum period.

Another potential cause of mortality is the relationship between the pregnant patient with portal hypertension and ruptured splenic artery aneurysm. This event can mimic other obstetric emergencies such as placental abruption, uterine rupture or an embolic event. Although the incidence in pregnancy is lower than in the general population (20 %), this may be explained in that many patients with portal hypertension rarely become pregnant [12].

We would recommend vaginal delivery under extradural analgesia with avoidance of any straining by the mother, which still allows progression to lower segment Caesarean section if necessary [13]. Treatment for active bleeding, including invasive monitoring, large-gauge cannulae, cross-matched blood, fresh frozen plasma, platelets, additional blood products, a Sengstaken–Blakemore tube and a vasopressin infusion must be available.

To avoid straining the most effective analgesia is ideally extradural analgesia with elective forceps or Ventouse extraction in the second stage. There should be no contraindications to extradural analgesia. One previous study described a pregnant patient with oesophageal varices secondary to portal hypertension from chronic schistosomiasis who also had thrombocytopenia. This patient had a splenectomy during pregnancy and this allowed an extradural to be performed for delivery [7]. Alternatively, delivery by forceps at commencement of the second stage using pudendal block anaesthesia has been reported, although the forceps delivery itself can be difficult if the head is still relatively high or in the occipito–posterior position, or both. This should avoid the marked increase in portal pressure which occurs in the second stage. Even in normal patients, contraction of the diaphragm can raise portal pressure to three times normal [14].

It is recognized that with portal hypertension and oesophageal varices the already engorged extradural veins of pregnancy may be dilated further. This increases the risk of a "bloody tap" when siting the extradural. Apart from positioning the patient in the lateral position for the procedure, and possible slight head-down tilt to reduce extradural vein pressure, there is little to reduce this problem. With extradural vein engorgement, the possibility of vascular absorption of the local anaesthetic with systemic toxic reaction could be increased. However, a study of extradural anaesthesia in patients with portal hypertension (although using mepivacaine rather than bupivacaine) did not show an increased risk [15].

Extradural analgesia was commenced in our patient with a dilute solution containing 0.1 % plain bupivacaine and fentanyl 2 $\mu g\ ml^{-1}$. Early in labour this produced good analgesia with a degree of independence of movement in the patient. As labour progressed, this mixture did not eliminate completely the desire to perform a Valsalva manoeuvre with the onset of each contraction and so this was changed to 0.25 % plain bupivacaine. This prevented the patient mobilizing but achieved the objective of removing any attempt to strain.

We believe lower segment Caesarean section should be reserved for obstetric indications [16–18] and where there is a contraindication to extradural anaesthesia. Theoretical advantages include a planned, elective time of delivery and possibly easier manipulation of the cardiovascular system under general anaesthesia. However, because of portal hypertension there may be dilated, aberrant vessels at Caesarean section, or adhesions from previous shunt surgery, and haemorrhage with hypotension may be as much a problem as the risk of hypertension. If a general anaesthetic is given, the patient should be treated as having a "full stomach" which usually involves extubation of the trachea with the patient awake and in the lateral position.

Spinal anaesthesia should probably be avoided as the block is usually dense, and hypotension from sympathetic block often occurs. Ephedrine may counteract this but it may cause tachycardia and hypertension. However, if ephedrine is avoided in this type of patient and further haemorrhage occurs then the subsequent hypotension may be profound.

Combined spinal and extradural anaesthesia can produce satisfactory analgesia with maintenance of some mobility, even if this is the ability to move around the bed rather than the labour ward. However, in extrahepatic portal hypertension the potential for some of the local anaesthetic required for the extradural to spread through the small dural puncture is even higher than usual [19] because of engorged extradural veins. The risk of a total spinal would further complicate the management of this patient.

The active management of the third stage with Syntometrine is to reduce the risk of postpartum haemorrhage. However, in this situation the potential effect of more forceful, iatrogenic, uterine contraction squeezing a larger blood volume to the inferior vena cava and then to the oesophageal varices was considered to outweigh that of haemorrhage. We allowed a physiological third stage as our patient's uterine contraction was effective.

Despite provision for a potentially serious outcome, this patient's antenatal and postnatal care were without incident. There is an argument for delivery of such a mother in a specialized obstetric–liver unit but this patient was extremely reluctant to travel outside the local vicinity. She had portal hypertension but no evidence of hepatic failure. Mandatory specialist referral is indicated in such cases for hepatic encephalopathy (grade 2–4), elevated prothrombin ratio (> 2 times normal control), metabolic acidosis (blood pH < 7.3), hypotension, hyponatraemia and thrombocytopenia. These features were not present in our patient.

References

1. Varma RR, Michelson NH, Borkowf HI, Lewis JD. Pregnancy in cirrhotic and non cirrhotic portal hypertension. *Obstetrics and Gynecology* 1977; **50**: 217–222.
2. Sherlock S. *Diseases of the Liver and Biliary System*, 8th Edn. London: Blackwell Scientific Publications, 1989.
3. Shearman DJC, Finlayson NDC. *Diseases of the Gastrointestinal Tract and Liver*. Edinburgh: Churchill Livingstone, 1982.
4. Schreyerp P, Caspi E, El-hindi JM, Eschar J. Cirrhosis–pregnancy and delivery: A review. *Obstetrical and Gynecological Survey* 1982; **37**: 304–312.
5. Scott DB, Kerr MG. Inferior vena cava pressure in late pregnancy. *Journal of Obstetrics and Gynaecology of British Commonwealth* 1963; **70**: 1044.
6. Kerr MG, Scott DB, Samuel E. Studies of the inferior vena cava in late pregnancy. *British Medical Journal* 1964; **1**: 532–533.
7. Soto-albors CE, Rayburn WF, Taylor L, Musselman M. Portal hypertension and hypersplenism in pregnancy secondary to chronic schistomiasis. A case report. *Journal of Reproductive Medicine* 1984; **29**: 345–348.
8. Britton CB. Pregnancy and esophageal varices. *American Journal of Surgery* 1982; **143**: 421–425.
9. Pozzi R, Ferenci P, Gangl A. Endoscopic sclerotherapy of oesophageal varices during pregnancy—case report. *Zeitschrift fur Gastroenterologie* 1991; **29**: 246–247.
10. Iwase H, Morise K, Kawase T, Horiuchi Y. Endoscopic injection sclerotherapy for esophageal varices during pregnancy. *Journal of Clinical Gastroenterology* 1994; **18**: 80–83.
11. Pauzner D, Wolman I, Niv D, Ber A, David MP. Endoscopic sclerotherapy in extrahepatic portal hypertension in pregnancy. *American Journal of Obstetrics and Gynecology* 1991; **164**: 152–153.
12. Barrett JM, Caldwell BH. Association of portal hypertension and ruptured splenic artery aneurysm in pregnancy. *Obstetrics and Gynecology* 1981; **57**: 255–257.
13. Teisala K, Tuimala R. Pregnancy and oesophageal varices. *Annals Chirurgiae et Gynaecologiae* 1985; **74**: 65–66.
14. Gordon AG, Johnston GW. Portal hypertension in pregnancy. *Journal of Obstetrics and Gynaecology* 1963; **70**: 1056–1059.
15. Arai Y, Oda T, Sameshima T, Miyao J, Yoshimura N. Application of epidural anaesthesia to portal hypertensive patients. *Japanese Journal of Anaesthesiology* 1981; **30**: 384–389.
16. Oyarzun E, Gonzalez R, Vesperinas G, Macaya R, Gomez R, Llanos O. Pregnancy and portal hypertension. *Revista Medica de Chile* 1993; **121**: 548–552.
17. Cheng Y-S. Pregnancy in liver cirrhosis and/or portal hypertension. *American Journal of Obstetrics and Gynecology* 1977; **128**: 812–822.
18. De Swiet. *Medical Disorders in Obstetric Practice*, 2nd Edn. London: Blackwell Scientific Publications, 1989.
19. Robbins PM, Fernando R, Lim GH. Accidental intrathecal insertion of an extradural catheter during combined spinal-extradural anaesthesia for Caesarean section. *British Journal of Anaesthesia* 1995; **75**: 355–357.

British Journal of Anaesthesia 1996; **76**: 328–329

Bilateral severe pain at L3–4 after spinal anaesthesia with hyperbaric 5% lignocaine

R. RODRÍGUEZ-CHINCHILLA, A. RODRÍGUEZ-PONT, T. PINTANEL AND F. VIDAL-LÓPEZ

Summary

We describe a case of transient pain in both legs after spinal anaesthesia with a hyperbaric solution of 5% lignocaine delivered in a single bolus through a 22-gauge Quincke needle. The patient remained in a supine decubitus position throughout surgery and 31 h later pain was referred bilaterally to the L3 and L4 dermatomes. (*Br. J. Anaesth.* 1996; **76**: 328–329)

Key words

Anaesthetic techniques, subarachnoid. Complications, neurological. Anaesthetics local, lignocaine.

Lignocaine 5% in hyperbaric solution has long been used for subarachnoid anaesthesia and was considered safe [1] until reports of permanent neurological complications began to appear in 1991, after the introduction of continuous spinal anaesthesia through microcatheters [2, 3]. Microcatheters were blamed mainly at first, until cases of severe transient pain in both lower extremities were reported later after spinal anaesthesia with 5% lignocaine in hyperbaric solution delivered in a single dose [4, 5]. We describe a case involving a patient who developed severe pain in both legs the second day after spinal anaesthesia with 5% lignocaine.

Case report

A 66-yr-old man, 159-cm tall and weighing 80 kg, was scheduled for removal of a penile implant that had caused skin ulceration. The patient had chronic bronchitis but there was no history of neurological problems. Blood clotting and chemistry were normal. Prior history included repair of an umbilical hernia, haemorrhoidectomy and implantation of a penile prosthesis on two occasions. Anaesthesia for all four operations comprised spinal injection of 0.5% bupivacaine. On this occasion, the patient was seated and the lumbar area washed with povidone. A spinal needle with a 22-gauge Quincke point was inserted easily at the L3–4 interspace. Correct placement was confirmed by free flow of CSF. We then administered 5% lignocaine 90 mg in a 7.5% glucose solution for subarachnoid anaesthesia (Laboratorios Palex SA, Barcelona, Spain) over a period of 10 s. The patient was awake during the spinal anaesthetic. There were no signs of pain or paresthesiae on insertion of the needle or during injection of the local anaesthetic and the patient was placed immediately in the supine decubitus position. Anaesthesia reached the T8 level and surgery lasted 35 min with no complications. Seventy minutes after injection of the anaesthetic, after signs of sensory and motor recovery had been observed, the patient was transferred to the ward. Thirty-one hours after surgery he complained of continuous burning pain perceived symmetrically on both sides from the hips to the popliteal fossa (L3–4). The pain was unaffected by change in position and no loss of strength or sensation was evident. There was no neck stiffness and no fever. The pain was not relieved by non-steroidal anti-inflammatory drugs (NSAID), heat pads or benzodiazepine compounds. The pain clinic was consulted and bilateral neuropathic pain, possibly related to subarachnoid anaesthesia, was diagnosed. Treatment with carbamazepine and metamizole, and a dose of amitriptyline at night, produced obvious improvement. This regimen was replaced by clonazepam and metamizole 24 h later, when dysarthria appeared. After 2 days on this treatment, and 4 days after anaesthesia, the pain disappeared completely and the patient was discharged 6 days after surgery with no sequelae.

Discussion

Neurological complications of subarachnoid anaesthesia are rare but potentially serious and at times difficult to diagnose. There are various causes, including direct neural damage by puncture, infections, haematomas, ischaemia caused by hypotension or other factors such as vasoconstriction or root distension [6]. The usual local anaesthetics and doses used for spinal anaesthesia are considered safe and have rarely been blamed for complications. Major neurological problems are rare; in 65000 operations with intradural anaesthesia, Kane [7] found only 16 such events, ranging from cases of mononeuropathy to lesions of the lumbar plexus. However, in another prospective study of 10098 cases of spinal anaesthesia in which the authors recorded minor neurological complications [8], pain identical to that seen after general anaesthesia in the lower extremities was found in 1% of cases.

ROBERT RODRÍGUEZ-CHINCHILLA, MD, ANNA RODRÍGUEZ-PONT, MD, TERESA PINTANEL, MD, FERNANDO VIDAL-LÓPEZ, MD, Department of Anaesthesia, Hospital Germans Trias i Pujol, Carretera del Canyet, s/n 08916 Badalona, Barcelona. Accepted for publication: October 5, 1995.

Correspondence to R.R.-C.

The safety of hyperbaric 5% lignocaine began to be questioned by Schneider and colleagues [4], who reported four cases of pain in the lower extremities (L5–S1) after spinal anaesthesia with single doses through a needle. The authors emphasized the possibility that the lithotomy position may have played a role, given that in dissections in that position the L5–S1 roots were lower and distended. A similar case was reported recently by Sjöström and Blåss [5].

Our case differed from the previous reported cases of transient lumbosacral neuropathy in that the patient was placed in the supine decubitus position, the affected roots were L3 and L4, and the pain appeared later and was relieved by antidepressants and anticonvulsants. The symmetrical nature of the pain and the lack of pain or paraesthesiae during the procedure suggests that no damage was caused by the needle. There was no hypotension or hypoxia that might have led to medullary ischaemia and the anaesthetic did not contain adrenaline. Chemical contamination was highly unlikely as we used disposable equipment and strict aseptic procedures. A single injection of hyperbaric 5% lignocaine was administered at the recommended dose for subarachnoid anaesthesia [6]. Moreover, a 22-gauge needle was used, and therefore overdose or poor distribution because of slow injection seems unlikely to have caused the complication. Our patient's pain was at the L3 and L4 dermatomes but, in all previously reported cases, patients were placed in the lithotomy position and L5 and S1 were always affected. We do not know what role the supine decubitus position or other factors may have played in producing the highly unusual location of our patient's lesion.

In nine of 11 cases of cauda equina syndrome described in the literature and in six cases of transient lumbosacral neuropathy, including the one described here, the only agent clearly implicated is hyperbaric 5% lignocaine, although these complications have been observed in animal studies after subarachnoid anaesthesia with 2-chloroprocaine and bupivacaine in clinical concentrations [9, 10]. In another study in rats, sensory deficit lasted longer in the group receiving 5% lignocaine in 7.5% glucose than in groups receiving 0.75% bupivacaine in 8.25% glucose, 5% amethocaine with 5% glucose or saline solution [11]. Similarly, in the same experimental model, it was shown that the presence of 7.5% glucose did not affect the ability of 5% lignocaine to produce sensory deficits [12].

The possibility of developing minor, transient neuropathy after subarachnoid anaesthesia should not be underestimated, given that the responsibility for follow-up and treatment of pain belongs to the anaesthetist. Pain therapy was different in all cases; three of the patients were relieved by NSAID, another by pethidine and one patient refused to take analgesics [4, 5]. Our patient also received NSAID but he was not relieved of pain until antidepressants and anticonvulsants were added. We believe that the clinical picture described here occurs more often than the literature suggests, but, as the condition unfolds 24 h after surgery, it often remains undiagnosed.

We believe that the use of hyperbaric 5% lignocaine for subarachnoid anaesthesia is not risk-free when given in a single dose through a large-calibre needle or when a position other than lithotomy is used. We conclude that its clinical use should be questioned and further studies should be performed.

References

1. Phillips OC, Ebner H, Nelson AT, Black MH. Neurologic complications following spinal anesthesia with lidocaine: a prospective review of 10440 cases. *Anesthesiology* 1969; **30**: 284–289.
2. Schell RM, Brauer FS, Cole DJ, Applegate RL. Persistent sacral nerve root deficits after continuous spinal anaesthesia. *Canadian Journal of Anaesthesia* 1991; **38**: 908–911.
3. Rigler ML, Drasner K, Krejcie TC, Yelich SJ, Scholnick FT, DeFontes J, Bohner D. Cauda equina syndrome after continuous spinal anesthesia. *Anesthesia and Analgesia* 1991; **72**: 275–281.
4. Schneider M, Ettlin T, Kaufmann M, Schuhmacher P, Urwyler A, Hampl K, von Hochstetter A. Transient neurologic toxicity after hyperbaric subarachnoidal anesthesia with 5% lidocaine. *Anesthesia and Analgesia* 1993; **76**: 1154–1157.
5. Sjöström S, Blåss J. Severe pain in both legs after spinal anaesthesia with hyperbaric 5% lignocaine solution. *Anaesthesia* 1994; **49**: 700–702.
6. Cousins MJ, Bromage PO. Epidural neural blockade. In: Cousins MJ, Bridenbaugh PO, eds. *Clinical Anesthesia and Management of Pain,* 2nd Edn. Philadelphia: JB Lippincott Company, 1988: 340–342.
7. Kane RE. Neurologic deficits following epidural or spinal anesthesia. *Anesthesia and Analgesia* 1981; **60**: 150–161.
8. Vandam LD, Dripps RD. A long-term follow-up of 10098 spinal anesthetics. II. Incidence and analysis of minor sensory neurological defects. *Surgery* 1955; **38**: 463–469.
9. Rosen MA, Baysinger CL, Shnider SM, Dailey PA, Norton M, Curtis JD, Collins M, Davis RL. Evaluation of neurotoxicity after subarachnoid injection of large volumes of local anesthetic solutions. *Anesthesia and Analgesia* 1983; **62**: 802–808.
10. Li DF, Bahar M, Cole G, Rosen M. Neurological toxicity of the subarachnoid infusion of bupivacaine, lignocaine or 2-chloroprocaine in the rat. *British Journal of Anaesthesia* 1985; **57**: 424–429.
11. Drasner K, Sakura S, Chan VWS, Bollen AW, Ciriales R. Persistent sacral sensory deficit induced by intrathecal local anesthetic infusion in the rat. *Anesthesiology* 1994; **80**: 847–852.
12. Sakura S, Chan VWS, Ciriales R, Drasner K. The addition of 7.5% glucose does not alter the neurotoxicity of 5% lidocaine administered intrathecally in the rat. *Anesthesiology* 1995; **82**: 236–240.

British Journal of Anaesthesia 1996; **76**: 330–331

Pulsed saline lavage causing venous air embolism in a patient with Paget's disease

C. A. SIDES

Summary

Pulsed saline lavage is used to prepare bony surfaces during joint replacement surgery. A patient is described in whom a venous air embolism occurred as a result of a combination of the increased vascularity of bone seen in Paget's disease and possible air entrainment in the lavage equipment. (*Br. J. Anaesth.* 1996; **76**: 330–331)

Key words

Complications, embolism. Embolism, air. Complications, Paget's disease.

Case report

A 71-yr-old man presented for a left cemented Furlong hip replacement to replace an arthritic hip joint. He also suffered from Paget's disease (osteitis deformans) involving the shaft of his femur and mild chronic obstructive airways disease (COAD). Physical examination was unremarkable except for some basal crepitations consistent with his COAD.

Spinal anaesthesia was produced with 0.5 % heavy bupivacaine 3 ml at the L2–3 interspace with a 22-gauge Whitacre needle after preloading with 0.9 % saline 500 ml. Oxygen was supplied via nasal cannulae at 2 litre min^{-1} while the patient listened to music via headphones.

Monitoring included non-invasive arterial pressure, electrocardiography, pulse oximetry and verbal contact. Surgery performed in the supine position proceeded uneventfully for the first 100 min, including reaming and cementation of the acetabular component of the joint replacement.

Surgical preparation included use of a Stryker Ortholav pulsed lavage system to irrigate and clean the bony surfaces before cementation. The lavage tip was inserted deep into the femoral shaft such that the outer suction channel was in direct contact with the perimeter of the canal. During femoral lavage the patient complained of feeling unwell with the sudden onset of dyspnoea and coughing. This was associated with a reduction in systolic arterial pressure from approximately 125 to 65 mm Hg, heart rate decreased to 65 beat min^{-1} after a brief tachycardia of 115 beat min^{-1} and peripheral arterial oxygen saturation decreased from 95 % to 88 %. A provisional diagnosis of venous air embolism (VAE) was made and treatment consisted of i.v. morphine and ephedrine and changing his nasal cannulae to a face mask and 100 % oxygen. The nature of the operation precluded turning the patient into the classic left lateral position. His cardiorespiratory variables improved to allow cementation and completion of the operation.

Postoperative recovery was uneventful with no evidence of either myocardial, pulmonary or cerebral sequelae.

Discussion

Embolization during hip surgery, of air, surgical debris or cement, particularly during impaction of the femoral component, is well recognized and may occur in up to 30 % of cases [1]. Lavaging the bone and venting the shaft help to minimize these risks. Pulsed lavage uses a peristaltic pump to force saline through connecting tubing and then through a coaxial lavage cannula, the inner tube of which has four side holes at the tip to provide a spray action. The saline and debris are aspirated through the outer tube which is set slightly proximal to the tip and connected to a normal theatre suction apparatus. The Ortholav pump is capable of generating up to 4.7 Barr and a flow of 900 ml min^{-1}. The lavage system operates regardless of the efficiency of the suction apparatus which can be reduced by the presence of large pieces of debris in the tubing.

Normal use of the pulsed lavage may have occluded the stem of the femur and any air trapped distally would have been forced into the femur. A similar event is thought to have occurred during pulsed irrigation of a perineal lesion in a patient with an open pelvic fracture in which trapped air was forced into the venous circulation with subsequent cardiovascular collapse [2]. In the case described here, the volume of air involved would be unlikely to have produced clinical symptoms. The second possible cause related to the lavage system itself. During lavage the saline bag was changed and activation of the machine at this time entrained air into the tubing which was then forced into the femur. During normal use this would not cause problems as the air would be either aspirated into the tubing or vented to the atmosphere but in the presence of a tight seal between the lavage cannula and the femoral canal and an inadequate aspiration system, this could lead to high pressures of air in the femoral shaft with subsequent embolization. The

---

C. A. SIDES MB, CHB, FRCA, Department of Anaesthesia, Bradford Royal Infirmary, Duckworth Lane, Bradford BD9 6RJ. Accepted for publication: September 5, 1995.

possibility of air being entrained in the tubing was demonstrated after operation and confirmed by the manufacturers. Rapid recovery would be consistent with an isolated event. A similar episode has been described during dental implant surgery when inadvertent injection of a mixture of air and water, passing through the hollow dental drill and directly into the mandible, caused death in three patients [3]. A VAE has been reported when injecting air into a femoral bone cyst during an attempt to aspirate it [4], so the increased vascularity seen in Paget's disease may have made such absorption more likely.

VAE is associated classically with anaesthetized patients undergoing neurosurgical procedures in the sitting position and diagnosis is based on end-tidal carbon dioxide measurements or precordial Doppler monitoring. In this case the latter was not available and the first sign was the patient complaining of breathlessness. The fact that the patient was under central neural block and not receiving nitrous oxide which, in anaesthetic concentrations, increases bubble size by between 200 % and 400 %, probably contributed to the fortunate outcome. Central venous cannulation is not used routinely but might have been helpful to aspirate any atrial collection of air.

The use of pulsed lavage systems is not universal and it is thought that there are about 120 units in use in the UK of which approximately 50 % are supplied by Stryker. The potential for significant VAE during the use of pulsed saline lavage should be remembered, especially in patients who may be at a higher risk of developing this complication, such as those suffering from Paget's disease. Care should be taken to ensure that air is not entrained in the lavage tubing and the aspiration system is functioning efficiently.

References

1. Michel R. Air embolism in hip surgery. *Anaesthesia* 1980; **35**: 858–862.
2. Brunicardi FC, Scalea TM, Bernstein MO, Sclafani SS, Phillips TF. Air embolism during pulsed saline irrigation of an open pelvic fracture: Case report. *Journal of Trauma* 1989; **29**: 700–701.
3. Davies JM, Campbell LA. Fatal air embolism during dental implant surgery: a report of three cases. *Canadian Journal of Anaesthesia* 1990; **37**: 112–121.
4. Rusheen JM, Hsu D, Lee C, Lippman M. Venous air embolism during surgical manipulation of a femoral bone cyst. *Anesthesiology* 1990; **72**: 200–201.

British Journal of Anaesthesia 1996; **76**: 332–337

CORRESPONDENCE

Inadvertent infusion of glucose saline into the extradural space

Sir,—A 10-yr-old girl with scoliosis underwent corrective surgery during general anaesthesia combined with a continuous thoracic extradural. During surgery she received extradural fentanyl 4 μg ml^{-1} which was continued after operation. Anaesthesia and surgery were uneventful. After operation the extradural infusion was set at 2–6 ml h^{-1} and she had satisfactory pain control. On the third day after operation the patient started complaining of inadequate analgesia. The extradural fentanyl syringe was infusing at 6 ml h^{-1}, as ordered. In addition, a three-way tap was connected to the extradural infusion set adjacent to the extradural filter. The third limb of the three-way tap was connected to the infusion of glucose saline (0.9 % NaCl and 225 % glucose with potassium chloride 20 mmol) 21 ml h^{-1}. The glucose saline infusion which was intended for i.v. infusion had been in progress for at least 1 h. The extradural was discontinued immediately. The patient had no sensory or motor symptoms and daily assessment of the patient for up to 2 weeks after the incident showed no evidence of neurological deficit. Her subsequent course was uneventful and she was discharged from hospital 3 weeks later.

This report illustrates yet another potential hazard of providing postoperative analgesia via infusion of opioids or opioids into the extradural space. The incidence emphasizes the necessity that nurses caring for extradural infusions be adequately trained, and that the responsible physicians visit these patients routinely to supervise this aspect of care.

There have been previous reports of substances other than those intended being infused into the extradural space [1, 2]. However, I could not find any other reports involving inclusion of a three-way tap to the extradural infusion set.

T. Mphanza
Department of Anaesthesia
Riyadh Military Hospital
Saudi Arabia

1. Tessler MJ, White I, Naugler-Colville M, Biehl DR. Inadvertent epidural administration of potassium chloride. *Canadian Journal of Anaesthesia* 1988; 35: 631–633.
2. Bickler P, Spears R, McKay W. Intralipid solution mistakenly infused into epidural space. *Anesthesia and Analgesia* 1990; 71: 712–723.

Cardiac arrest at induction of anaesthesia for Caesarean section

Sir,—I wish to comment on the case report of a cardiac arrest at induction of anaesthesia for Caesarean section by McIndoe, Hammond and Babington [1]. They ascribed the cardiac arrest to peripartum cardiomyopathy and dismissed an anaphylactic reaction as unlikely.

There are reasons to suggest that an anaphylactic reaction was a likely cause of the patient's cardiac arrest instead of peripartum cardiomyopathy. The patient had no symptoms or signs of cardiac disease before induction of anaesthesia, which is unusual in cases of peripartum cardiomyopathy. The cardiac arrest occurred at induction of anaesthesia with drugs known to precipitate anaphylaxis, and responded to treatment for asystolic cardiac arrest and anaphylaxis, which included adrenaline by bolus and then infusion. The arrhythmias noted (including bradycardia unresponsive to atropine) are recognized manifestations of anaphylaxis [2].

Initial intensive care assessment revealed few cardiovascular abnormalities but the case report described progressive development of symptoms, signs and imaging features of cardiac failure. Profound, reversible myocardial contractile depression attributed to anaphylaxis has been reported in two patients by Raper and Fisher [3]. One patient had been anaesthetized with thiopentone and alcuronium and the other had received a bee sting. Both required intra-aortic counterpulsation balloon pumping and inotropic support for several days. The extent of cardiac dysfunction was documented with pulmonary artery catheter monitoring, echocardiography and radionuclide ventriculography. Raper and Fisher attributed their patients' myocardial contractile depression directly to anaphylaxis. They pointed out that it can also be associated with hypotension, hypoxaemia and acidosis which often accompanies anaphylaxis, especially in patients with underlying cardiac disease.

It may be important for this woman's future anaesthetic and obstetric management if anaphylaxis is regarded as a possible cause for her cardiac arrest and subsequent clinical course.

J. A. Wilson
Department of Anaesthesia
Hammersmith Hospital
London

1. McIndoe AK, Hammond EJ, Babington PCB. Peripartum cardiomyopathy presenting as a cardiac arrest at induction of anaesthesia for emergency Caesarean section. *British Journal of Anaesthesia* 1995; 75: 97–101.
2. Assem ESK. Anaphylactic reactions affecting the human heart. *Agents and Actions* 1989; 27: 142–145.
3. Raper RF, Fisher MMcD. Profound reversible myocardial depression after anaphylaxis. *Lancet* 1988; 1: 386–388.

Sir,—We thank Dr Wilson for his letter regarding our recent case report on a cardiac arrest occurring at induction of anaesthesia for an emergency Caesarean section [1]. It can be difficult to differentiate between minor signs and symptoms of cardiac dysfunction in the latter stages of pregnancy and less than 10 % of patients with peripartum cardiomyopathy present before delivery. The distinction between anaphylactoid and anaphylactic reactions to anaesthetic agents depends on whether there is documented previous exposure to the agent. This distinction is becoming somewhat blurred and they may have similar pathophysiology. In this case the patient had previously been exposed to both thiopentone and suxamethonium. There was no family history or known sensitivity to anaesthetic agents.

Severe anaphylactic–anaphylactoid reactions to anaesthetic drugs are uncommon [2]. The clinical picture is usually one of hypotension, bronchospasm, acute urticarial skin rashes and varying degrees of cardiovascular instability, including brady-dysrhythmias. Myocardial dysfunction, although reported, is rare in patients without underlying disease [3, 4].

The timing of events in this case strongly suggested an anaphylactic–anaphylactoid response to agents used at induction, that is suxamethonium, thiopentone or i.v. ranitidine (given 20 min before induction). Therefore, the patient was treated initially for anaphylaxis following the Wessex Regional Anaphylaxis Procedure [5], with appropriate serum and urine specimens obtained for subsequent analysis. However, further review of the patient alerted our suspicions to the possibility of a primary myocardial problem rather than a drug reaction. Notably there was complete absence of any cutaneous or pulmonary signs of systemic histamine release. Cardiac failure occurred 6 h after the primary event. Myocardial dysfunction was documented by echocardiography when the patient was transferred to the care of the regional cardiology centre who confirmed the clinical suspicion of peripartum cardiomyopathy.

Subsequent analysis of serial samples obtained at the time of the event and at regular intervals over the hours after presentation (according to the Wessex Anaphylaxis Procedure) showed a negative tryptase test, negative RAST (radioallergosorbent test) to suxamethonium, normal IgE concentrations and normal urine methyl histamine concentrations. Collectively, these results do not support the argument that this patient suffered an anaphylactic–anaphylactoid reaction as there was no objective evidence of mast cell degranulation and histamine release.

In the light of serological data available, the consensus of opinion from the anaesthetist, cardiologist and immunologist involved with this case was a diagnosis of peripartum cardiomyopathy.

A. K. McIndoe
E. J. Hammond
Department of Anaesthesia
Princess Margaret Hospital
Swindon

1. McIndoe AK, Hammond EJ, Babington PCB. Peripartum cardiomyopathy presenting as a cardiac arrest at induction of anaesthesia for emergency Caesarean section. *British Journal of Anaesthesia* 1995; **75**: 97–101.
2. Watkins J. Adverse anaesthetic reaction. An update from a proposed national reporting and advisory service. *Anaesthesia* 1985; **40**: 797–800.
3. Fisher M. Anaphylactic cardiovascular collapse: Clinical observations on pathophysiology and treatment. *Anaesthesia and Intensive Care* 1986; **14**: 17–21.
4. Raper RF, Fisher MMcD. Profound reversible myocardial depression after anaphylaxis. *Lancet* 1988; **1**: 386–388.
5. *Anaphylactic Reactions Associated with Anaesthesia*. London: Association of Anaesthetists, 1990.

Day-case cataract surgery

Sir,—Every day thousands of elderly patients are operated on as day-cases during general anaesthesia. Why is it only in ophthalmology departments that the only alternatives considered are inpatient surgery with general anaesthesia or day-case surgery with local anaesthesia [1]. This opinion was continued by Whitehead [2] in reply to the article of Moffatt and Cullen [1]. If the patient is suitable for day-case surgery, the mode of anaesthetic is irrelevant and can be left to patient preference. A short general anaesthetic for eye surgery is not traumatic or physiologically disturbing and will hardly delay discharge. Please do not encourage this continued attitude which excludes this large group from routine day-case surgery under general anaesthesia.

J. E. Goold
Department of Anaesthetics
Queen Elizabeth Hospital
Welwyn Garden City
Hertfordshire

1. Moffat A, Cullen PM. Comparison of two standard techniques of general anaesthesia for day-case cataract surgery. *British Journal of Anaesthesia* 1995; **74**: 145–148.
2. Whitehead PN. General anaesthesia for day-care cataract surgery. *British Journal of Anaesthesia* 1995; **75**: 252–253.

Sir,—We support Whitehead's 6 months' experience with a local anaesthetic management regimen for day-case cataract surgery [1].

Since 1984, regional–local anaesthetic techniques have been used for more than 39500 cataract extraction–lens implantation procedures at the Gimbel Eye Centre, Calgary [2] with postoperative discharge within 1 h. An additional advantage of these techniques, especially for diabetic patients, is that patients may continue with their normal diet before operation on the day of surgery [3]. General anaesthesia was used in 0.025 % of all cases; three adults in whom the indications were allergy to eye drops, severe coarse head tremor and mental handicap, and 93 children. None of the patients required admission to hospital. During the same period in Foothills Hospital, Calgary, regional–local anaesthesia was used in 99 % of 11000 adults, the remaining 1 % undergoing general anaesthesia, usually for patient preference.

During this time, there were three deaths in more than 50000 cases. One hospital patient, an obese 75-yr-old woman, suffered sudden cardiovascular collapse 20 min after retrobulbar block. Unlike patients in whom brain stem anaesthesia occurs [4], she could not be resuscitated. Pulmonary embolism was suspected because the patient had fallen 3 days earlier and bruised her leg. However, permission for autopsy was refused. Two elderly patients who had undergone regional anaesthesia at the Gimbel Eye Centre died after operation from acute myocardial infarction, one at 48 h and the other at 5 days. Although we have no data for a comparable group during general anaesthesia, we believe that this mortality rate is not unexpected, considering the physical status of many elderly cataract patients who suffer from concomitant systemic disease.

J. R. Maltby
R. C. Hamilton
R. G. Loken
Department of Anaesthesia
University of Calgary
Calgary, Alberta, Canada

1. Whitehead PN. General anaesthesia for day-case cataract surgery. *British Journal of Anaesthesia* 1995; **75**: 252–253.
2. Hamilton RC, Gimbel HV, Strunin L. Regional anaesthesia for 12000 cataract extraction and intraocular lens implantation procedures. *Canadian Journal of Anaesthesia* 1988; **35**: 615–623.
3. Maltby JR, Hamilton RC. Preoperative fasting guidelines for cataract surgery under regional anaesthesia. *British Journal of Anaesthesia* 1993; **71**: 167.
4. Hamilton RC. Brain-stem anaesthesia as a complication of regional anaesthesia for ophthalmology. *Canadian Journal of Ophthalmology* 1992; **27**: 323–325.

Effects of propofol on rabbit mesenteric arteries and veins

Sir,—I believe there are some problems with the article of Kamitani and colleagues [1]. First, there appears to be a mistake in the results section concerning the effects of propofol on noradrenaline-induced contraction, which states "...propofol 3×10^{-6} mol litre^{-1} significantly dilated the mesenteric artery without endothelium." This does not agree with figure 1, and I would suggest that what was meant was that propofol 3×10^{-5} mol litre^{-1} significantly constricted the mesenteric artery without endothelium. This would agree with the summary.

Similarly, in the section concerning the effect of propofol on K$^+$-induced contraction, the authors state "... in concentrations of 3×10^{-6} to 3×10^{-5} mol litre^{-1}, propofol significantly dilated the denuded mesenteric arteries ...". This does not agree with figure 2 which suggests that certainly no dilatation, but perhaps a small amount of contraction occurred.

In their final sentence the authors concluded that this study "suggested that vasoconstriction of noradrenaline-induced arterial contraction by propofol was caused by the inhibition of EDRF from the endothelium". This cannot be the whole story as constriction was maximal in arteries where there was no endothelium, and therefore no EDRF (nitric oxide) to inhibit. This study certainly adds support to the previous suggestion, cited by the authors [2], that propofol may inhibit the synthesis or action of EDRF. However, it seems more likely that the vasoconstricting action of very low concentrations of propofol in this model was caused by a direct action of propofol on the arterial smooth muscle cells. The fact that the vasoconstriction was less in intact than in denuded arteries supports the contention that EDRF might in fact oppose the vasoconstricting effect of propofol.

N. Stratford
Sir Humphry Davy Department of Anaesthesia
Bristol Royal Infirmary
Bristol

1. Kamitani K, Yamazaki M, Yukitaka M, Ito Y, Momose Y. Effects of propofol on isolated rabbit mesenteric arteries and veins. *British Journal of Anaesthesia* 1995; **75**: 457–461.
2. Park WK, Lynch C, Johns RA. Effects of propofol and thiopental in isolated rat aorta and pulmonary artery. *Anesthesiology* 1992; **77**: 956–963.

Sir,—I appreciate the letter by Dr Stratford which relates to our article.

We agree with Dr Stratford that there were several errors in our article and we regret these errors. In the results section, 3×10^{-6} mol litre^{-1} is apparently a typographical error, and should read 3×10^{-5} mol litre^{-1}. Also, the word "dilated" as he pointed out, should read "constricted". Therefore, we should state that: "propofol *3×10^{-5} mol litre^{-1}* significantly *constricted* the mesenteric artery without endothelium" in the noradrenaline-induced contraction section, and "in concentrations of 3×10^{-6} to 3×10^{-5} mol litre^{-1}, propofol significantly *constricted* the denuded mesenteric arteries" in the K$^+$-induced contraction section. As Dr Stratford suggested, the vasoconstricting action of low concentrations of propofol is likely to be caused by a direct action of propofol on arterial smooth cells.

Thank you for the opportunity to correct these errors.

K. Kamitani
Toyama Medical and Pharmaceutical University
Sugitani, Toyama, Japan

A pitfall in the use of the Altman nomogram for power estimation

Sir,—We wish to draw attention to a pitfall in using Altman's nomogram [1] (or any equivalent method) for deciding the number of patients that need to be included in a clinical trial to ensure that it has adequate power, that is adequate probability of detecting a clinically important difference between two treatments. We encountered the problem when conducting a parallel-group trial to see if piroxicam, given before operation, reduced postoperative consumption of morphine in adults undergoing tonsillectomy.

To enter the Altman nomogram it is necessary to determine the "standardized difference": the minimum clinically important difference in the effect of the two treatments divided by the standard deviation (SD) between patients. We decided that a one-third reduction in morphine use would be worthwhile and obtained an SD of morphine usage following piroxicam in hip replacement of 40% of the mean [2]. Therefore, assuming that this percentage SD would apply to our patients, we calculated a standardized difference of $33\%/40\% = 0.8$. The nomogram then predicted the need for a total of 50 patients for a power of 0.8 at $P = 0.05$.

When the study was completed, morphine use in the piroxicam group was indeed almost one-third less than in the control group, but the SD between patients in our groups was not 40% but 90%! Therefore it is not surprising that our result was not significant, even allowing for the lower power [3] of the Mann–Whitney test that was needed because of the very skew distribution.

The essential message is that, in seeking a relevant estimate of the SD from the literature, it is not sufficient (and perhaps not necessary) to find a study that has tested the effect of the same treatment; what is needed is a study in which the SD of the outcome variable is likely to be the same as in the new study.

For example, a recent comparison of ketorolac and acetaminophen during tonsillectomy [4] used postoperative consumption of morphine as an outcome variable and reported SD values of 110%. The circumstances were somewhat different from those in our study and so the implications are a little ambiguous. However, if we had possessed that information at the time, we would certainly have been more cautious in our planning.

We have had to present this argument in terms of percent SD because the data demanded it; but clearly the problem would be exactly the same where absolute SD values were relevant. The SD culled from the literature must be relevant to the circumstances of the new study.

M. J. Evans
Department of Anaesthetics
Glan Clwyd District Hospital
Bodelwyddan, Rhyl
C. A. Harrison
Department of Anaesthetics
Nevill Hall Hospital
Abergavenny
W. W. Mapleson
Department of Anaesthetics and Intensive Care Medicine
University of Wales College of Medicine
Cardiff

1. Altman DG. Statistics and ethics in medical research, III. How large a sample? *British Medical Journal* 1980; **281**: 1336–1338.
2. Serpell MG, Thomson MF. Comparison of piroxicam with placebo in the management of pain after total hip replacement. *British Journal of Anaesthesia* 1989; **63**: 354–356.
3. Siegel S, Castellan NJ, jr. *Nonparametric Statistics for the Behavioral Sciences*, 2nd Edn. New York: McGraw-Hill, 1988; 137.
4. Rusy LM, Houck CS, Sullivan LJ, Ohlms LA, Jones DT, McGill TJ, Berde CB. A double-blind evaluation of ketorolac tromethamine versus acetaminophen in pediatric tonsillectomy: analgesia and bleeding. *Anesthesia and Analgesia* 1995; **80**: 226–229.

Change in neostigmine ampoules

Sir,—We are extremely distressed by the decision of Roche (UK) to discontinue the production of Prostigmin ampoules (neostigmine 0.5 mg in 1 ml) and in particular with the method of withdrawal, with no prior warning or discussion. More and more paediatric patients are from the smaller end of the spectrum of weights, because of the successes of neonatal intensive care. Diluting drugs to the extent needed is both inherently dangerous and inaccurate for a drug with a precise dosage. A dilution of 1:10 of the adult 2.5-mg ampoule results in a suitable dose only for a child more than 5 kg in weight. At a time when risk management and patient safety are uppermost in our minds, decisions such as this by drug companies, made for presumably purely financial reasons, must be resisted strenuously by the profession.

A. M. Mackersie
Department of Anaesthesia
Great Ormond Street Hospital for Children NHS Trust
London

Volume preloading, spinal anaesthesia and Caesarean section

Sir,—I was interested to read the editorial and article on the subject of volume preloading before spinal block for Caesarean section [1, 2].

The authors of the article demonstrated that administration of fluids in the form of 1000 ml of crystalloid solution had no influence on the incidence, severity or duration of hypotension after extradural block. They have now abandoned the routine of preloading before regional anaesthesia. Before this message is acted upon may I suggest that the findings do not justify the conclusions and commend to all the advantages of preloading, as supported in your editorial.

Spinal anaesthesia results in peripheral vasodilatation and reduced systemic vascular resistance with frequent hypotension, which may or may not be accompanied by a reduction in cardiac output. Measurement of arterial pressure during anaesthetic procedures is universal and indeed it is considered negligent not to do so. However it is a poor substitute for what we should be measuring, that is cardiac output or oxygen delivery. It is clear that measurement of cardiac output in every patient is impracticable but until non-invasive, reproducible and accurate cardiac output measurement is available, we have to content ourselves with measurement of arterial pressure. Arterial pressure does not equate with cardiac output and taken in isolation is fairly meaningless. Statistically there is a poor correlation between arterial pressure and cardiac output ($r = 0.2$), as has been demonstrated by Reinhart [3].

Sivarajan and colleagues [4] have clearly demonstrated that low arterial pressure, in response to peripheral vasodilatation, can be accompanied by either an increase or decrease in cardiac output. Arterial pressure alone is not sufficient to indicate the state of cardiac output. Lawson and colleagues [5] have demonstrated that the directional change in cardiac output after the onset of hypotension secondary to vasodilatation depends on the preoperative intravascular volume. Low circulating blood volumes when associated with hypotension are accompanied by a low cardiac output following peripheral vasodilatation. Conversely, when adequate preload is available, hypotension can also be achieved by peripheral vasodilatation but without a reduction in cardiac output.

The importance of preinduction circulating volume before peripheral vasodilatation has also been demonstrated by Boon and co-workers [6]. These authors showed that the cardiac output response to vasodilatation with sodium nitroprusside depended on the state of the circulating volume. Cardiac output decreased in association with hypotension accompanying vasodilatation when the dogs were hypovolaemic but not when the animals were normovolaemic.

My own experience of approximately 1000 induced hypotensive anaesthetics using peripheral vasodilators supports this view. Preloading patients with 1 litre of crystalloid solution before reduction in arterial pressure avoids the reduction in $P\mathrm{E}_{CO_2}$ normally indicative of a decrease in cardiac output. In the absence of cardiac output measurement or capnography, I would suggest caution before adopting the recommendations of this article. Until these studies have been repeated while cardiac output is measured we should continue to preload patients and be very circumspect in how we interpret the often misleading results of measuring arterial pressure in isolation.

E. G. LAWES
Shackleton Department of Anaesthesia
Southampton University Hospitals
General Hospital
Southampton

1. Jackson R, Reid JA, Thorburn J. Volume preloading is not essential to prevent spinal-induced hypotension at Caesarean section. *British Journal of Anaesthesia* 1995; **75**: 262–265.
2. Rocke DA, Rout CC. Volume preloading, spinal hypotension and Caesarean section. *British Journal of Anaesthesia* 1995; **75**: 257–259.
3. Reinhart K. Principles and practice of SvO_2 monitoring. *Intensive Care World* 1988; **5**: 121–124.
4. Sivarajan M, Amory DW, Everett GB, Buffington C. Blood pressure, not cardiac output, determines blood loss during induced hypotension. *Anesthesia and Analgesia* 1980; **59**: 203–206.
5. Lawson NW, Thompson DS, Nelson CL, Flacke JW, North E. Sodium nitroprusside-induced hypotension for supine total hip replacement. *Anesthesia and Analgesia* 1976; **55**: 654.
6. Boon JC, Westbroek DL, Stelter WJ, Messmer K. Sodium nitroprusside-induced hypotension in dogs. Drug sensitivity and resistance experimentally provoked by circulating blood volume alterations. *European Surgical Research* 1978; **10**: 382–388.

Sir,—We read with interest the article by Jackson, Reid and Thorburn [1]. The results of their study on the apparent lack of efficacy of i.v. crystalloid hydration in preventing spinal-induced hypotension are difficult to interpret because they contradict routine clinical practice. We wish to comment on several points.

The authors used ephedrine 47.5 mg (mean) which appears to be higher than that used routinely to treat hypotension. Hauch and co-workers [2] used ephedrine i.v., as necessary, to treat hypotension after spinal anaesthesia and their average requirement was 18.8 mg. However, Hall and co-workers [3] used a combination of an initial bolus followed by an infusion to treat hypotension and their mean dose was 59 mg. In this study, prophylactic ephedrine 60 mg in Hartmann's solution 500 ml was administered via an ordinary infusion set. The high dose of ephedrine used may have been a result of manual adjustment of the infusion, or it is possible that rapid tachyphylaxis to ephedrine may have developed because of the method of administration.

Apgar score and biochemical variables such as umbilical pH measurements are not sensitive indicators of changes in utero-placental perfusion and may reflect only an early and crude assessment of global neonatal activity which can be affected by many other variables occurring at the time of delivery [4]. However, Ramin and co-workers [5] demonstrated significant fetal acidaemia after prophylactic infusions of ephedrine in spite of preloading. Neurobehavioural score [6], a sensitive indicator of fetal well-being, could have been used to assess the effect of such a high dose of ephedrine. Jouppilla and co-workers [7] showed that after i.v. preload, placental blood flow is better maintained. Also, methods to assess placental perfusion such as umbilical artery Doppler velocimetry [8] are useful.

In the unpreloaded group, Hartmann's solution 200 ml was administered over 10 min. This appears to be excessive solely for maintaining the patency of a cannula. In addition, Hartmann's solution 400 ml, containing ephedrine, was infused after spinal injection. Another 400 ml of crystalloid was administered in parallel with the ephedrine infusion, after spinal injection. In total, the authors used more than 1 litre of crystalloid in this group. In our opinion, this is merely shifting i.v. hydration from the period before spinal injection to that after injection.

The authors treated hypotensive episodes with bolus doses of ephedrine and fluid. If fluid overload is such a concern (although a case of pulmonary oedema has not yet been reported in the literature after spinal anaesthesia), why did they not treat the hypotension with ephedrine alone?

We feel that on the basis of this trial alone, it is neither possible to conclude that preload is not essential nor is it possible to recommend a change in clinical practice. Moreover, the incidence of hypotensive episodes was similar in both preloaded and unpreloaded groups. The conclusion that may be drawn from this study is that neither preloading nor prophylactic ephedrine infusion alone prevents hypotension after spinal anaesthesia in obstetric patients. A sensible approach would be that which we practise in this institution, of using ephedrine early, and keeping preload and perioperative i.v. fluids to a minimum, compatible with both maternal and fetal well-being.

A. MALLICK
A. SAMAAN
P. BRAITHWAITE
Department of Anaesthetics
Leeds General Infirmary
Leeds

1. Jackson R, Reid JA, Thorburn J. Volume preloading is not essential to prevent spinal-induced hypotension at Caesarean section. *British Journal of Anaesthesia* 1995; **75**: 262–265.
2. Hauch MA, Gaiser RR, Hartwell BL, Datta S. Maternal and fetal colloid osmotic pressure following fluid expansion during Cesarean section. *Critical Care Medicine* 1995; **23**: 510–514.
3. Hall PA, Bennett A, Wilkes MP, Lewis M. Spinal anaesthesia for Caesarean section: comparison of infusions of phenylephrine and ephedrine. *British Journal of Anaesthesia* 1994; **73**: 471–474.
4. Santos AC, Pedersen H. Current controversies in obstetric anesthesia. *Anesthesia and Analgesia* 1994; **78**: 753–760.
5. Ramin SM, Ramin KD, Cox K, Magness RR, Shearer VE, Norman FG. Comparison of prophylactic angiotensin II versus ephedrine infusion for prevention of maternal hypotension during spinal anesthesia. *American Journal of Obstetrics and Gynecology* 1994; **171**: 734–739.
6. Ratcliffe FM, Evans JM. Neonatal well-being after elective Caesarean delivery with general, spinal and epidural anaesthesia. *European Journal of Anaesthesiology* 1993; **10**: 175–187.
7. Jouppila P, Jouppila R, Barinoll T, Koivula A. Placental blood flow during Caesarean section performed under subarachnoid blockade. *British Journal of Anaesthesia* 1984; **56**: 1379.
8. Valli J, Pirhonen J, Aantaa R, Erkkola R, Kanto J. The effects of regional anaesthesia for Caesarean section on maternal and fetal blood flow velocities measured by Doppler ultrasound. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 165–169.

Sir,—We are gratified by the interest of Dr Lawes and Drs Mallick, Samaan and Braithwaite in our study, and thank you for the opportunity to reply.

We accept the risk of a type II error, but we selected our population carefully, as described in the text, to reduce patient variability. This inevitably had the consequence of introducing constraints such as the availability of adequate numbers of suitable patients within a reasonable period of time. The fact that the number and severity of hypotensive episodes were identical confirms the appropriateness of the study design.

We also agree that the relationship between cardiac output and arterial pressure is poor, and for this reason fetal acid–base balance assumes greater importance, and again, there was no difference between the two groups. There appears to be confusion between "hypovolaemia" and the effect of sympathetic block. Our patients were not hypovolaemic, indeed surgery was undertaken in the morning only, to ensure similar volaemic status among patients.

Preloading patients for elective Caesarean section and the prophylactic use or treatment with ephedrine by infusion is the standard regimen used in the prevention or management of maternal hypotension. There is, however, little agreement on what the optimum therapy is, and it was for this reason that the study was undertaken. It is also true that despite the variety of combinations of i.v. fluids and ephedrine in use, maternal hypotension after spinal anaesthesia remains a persistent problem. Many studies have demonstrated that neonatal acid–base balance is affected adversely by maternal hypotension, particularly if prolonged and is a readily obtained measure of adequate fetal perfusion. The role of neonatal neurobehavioural assessment in the presence or absence of maternal hypotension despite its use for over 21 years remains unproved, difficult to perform and requires resources which are not widely available.

Moving the rigid procedure of infusing i.v. fluid from the period before spinal injection to after injection represents the difference between prophylaxis against and treatment of the consequent sympathetic block, which was one of the aims of the study.

The combined use of preloading and infusion of ephedrine used in our study represents, in our view, standard practice. We agree with the final sentence of the letter of Drs Mallick, Samaan and Braithwaite, but what is the optimum dose of ephedrine, the volume of preload and the perioperative i.v. fluid load? We attempted to qualify the word "enough".

We have abandoned formal preloading, and our experience since adopting that approach has been reassuring, but we do infuse fluids when the block is developing and add ephedrine if hypotension develops.

Our article is now added to a growing number which question the validity of preloading in both pregnant and non-pregnant subjects with solutions which have an evanescent action. We await with interest the publication of larger studies. At present we are protecting our patients from infusion of large volumes of i.v. fluids, and the potential risk of delay in the emergency situation while waiting for a "suitable" preload volume to be infused. We too have had difficulty in coming to terms with changing the habits of a lifetime.

J. REID
J. THORBURN
Department of Anaesthesia
Queen Mother's Hospital
Glasgow

Accidental insertion of an extradural catheter

Sir,—We wish to support the authors Robbins, Fernando and Lim [1] on their finding that accidental insertion of an extradural catheter through a dural hole made by a spinal needle in the single space combined spinal extradural (CSE) technique may be more than a theoretical risk. Two similar cases have been reported briefly in the past [2] and we wish to report a similar case.

A 38-yr-old Asian woman was admitted for elective Caesarean section having required an emergency Caesarean section in a previous pregnancy. On arrival in the operating theatre, she received a preload of Hartmann's solution 1 litre and monitoring consisted of ECG, non-invasive arterial pressure and pulse oximetry.

A needle-through-needle CSE technique was carried out at L3–4 using a Portex 16-gauge Tuohy needle and a 24-gauge Sprotte needle. The procedure was carried out with the patient in the sitting position and the loss of resistance to air technique was used to identify the extradural space. The extradural space was located without difficulty and dural puncture with the Sprotte needle was confirmed by the sight of cerebral spinal fluid (CSF) at the hub of the spinal needle; 0.5% bupivacaine 2.5 ml with 8% glucose was injected. At the end of injection of the local anaesthetic, CSF could not be aspirated. After removal of the spinal needle and without rotating the Tuohy needle, an extradural catheter was threaded 3 cm into the extradural space. There was no CSF in the Tuohy needle and there was no resistance during the passage of the catheter. When the catheter had been secured, the patient was put onto her left side and turned onto her right side after 5 min. After 20 min, the patient had partial sensory block in her legs, no motor block and no sacral block. It was assumed at this stage that the spinal technique was unsuccessful. The decision was made to proceed to use the extradural catheter to provide extradural anaesthesia. After a negative aspiration test (aspiration through the filter after flushing the catheter with normal saline 1.5 ml to avoid an air lock [3]), a test dose of 2% lignocaine 3 ml with adrenaline 1:200000 was injected through the extradural catheter. Within 5 min, the patient developed bilateral motor and sensory block from T4 to S5. Aspiration of the catheter was attempted again but this gave a negative test. However, when the filter was disconnected and aspiration attempted once more, there was free flow of CSF. Dextrostix indicated a positive test for glucose (11–17 mmol litre^{-1}). This could have been caused by earlier injection of bupivacaine with glucose. The patient's blood glucose was 7 mmol litre^{-1}. After operation the catheter was left *in situ* and when sensation returned, plain bupivacaine 2.5 ml was injected through the catheter. This provided immediate pain relief with motor and sensory block from T12 to S5. At this stage, CSF was again easily aspirated and confirmed by a positive test for glucose (11–17 mmol litre^{-1}), 3 h having elapsed since the original injection of bupivacaine with glucose.

We believe that the extradural catheter had been placed accidentally in the subarachnoid space after the initial dural puncture was made by the Sprotte needle. Failure of the spinal technique could have been caused by relocation of the spinal needle to be partially in the extradural and subarachnoid spaces. It is less clear how placement of the catheter into the subarachnoid space occurred. One explanation could be that the catheter may have entered the subarachnoid space through the hole made by the spinal needle, a theory suggested by Robbins, Fernando and Lim. This would imply a catheter with an external diameter of 1.1 mm entering through a hole made by a needle with an external diameter of 0.55 mm. The second explanation is that a hole in the dura could have been made by the Tuohy needle. This was unlikely as there was no CSF visible through the Tuohy needle at the time of insertion and the Tuohy needle was not rotated between introducing the spinal needle and threading the catheter. The third explanation is that the end of the Tuohy needle may have been in the subdural space and placement of the catheter perforated the arachnoid mater and entered the subarachnoid space. The distance of approximately 7 mm between the end of the Tuohy needle and the side opening of the Sprotte needle when CSF was sighted would question this theory. Therefore, there is no clear explanation as to how the catheter came to lie in the subarachnoid space.

We were pleased to find on subsequent follow-up that, as in the case of Robbins, Fernando and Lim, our patient did not develop a post-dural puncture headache.

This case and those reported previously [1, 2] highlight the need to give a test dose after a CSE technique in order to exclude intrathecal placement of the catheter. As shown in our case, a negative aspiration test through the filter does not always exclude a catheter in the subarachnoid space. The use of CSE in obstetric anaesthetic practice is increasing and anaesthetists need to be aware of potential problems which may occur as their use becomes more widespread.

A. FOX
M. C. MUSHAMBI
Leicester Royal Infirmary
Leicester

1. Robbins PM, Fernando R, Lim GH. Accidental intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia for Caesarean section. *British Journal of Anaesthesia* 1995; **75**: 355–357.
2. Ferguson DJM. Dural puncture and epidural catheters. *Anaesthesia* 1992; **47**: 272.
3. Charlton GA, Lawes EG. The effect of micropore filters on the aspiration test in epidural analgesia. *Anaesthesia* 1991; **46**: 573–575.

Transoesophageal echocardiography in chest trauma

Sir,—Kennedy, Ireland and McConaghy [1] described a case of acute trauma, with death from uncontrollable bleeding from a thoracic source. They used transoesophageal echocardiography (TOE) to exclude pericardial effusion and diagnosed interatrial pathology. Unfortunately, they did not describe the equipment used, and it is therefore assumed that they used a single plane probe, presumably with no colour Doppler facility. The echocardiograms illustrated are presumably those taken before the initial laparotomy.

Both pictures in fact show marked echodense material anterior to the right atrium and right ventricle, consistent with (but not diagnostic of) clot and blood within the anterior aspect of the pericardial cavity. In addition, there is surprising bowing of the interatrial septum towards the left atrium, suggesting that the left atrial pressures were lower than the right (2–8 cm H_2O). In view of these, transthoracic echocardiography (TTE) would have been an essential additional assessment, despite its notorious difficulty in patients with an intubated trachea, as views of the anterior mediastinum are seen more clearly. In retrospect, it may be reasonable to assume that the right atrial pressures were not raised because the pericardium had already "opened", and blood in the posterior and lateral mediastinum had drained to the thorax.

With regard to the diagnosis of atrial septal rupture and haematoma on the echocardiographic evidence, many caveats need to be added. In the plane of examination of the four-chamber view, the interatrial septum is almost parallel to the ultrasound beam, and artefacts are not unusual. The standard biatrial view, where the interatrial septum is perpendicular to the beam is more reliable [2]. The superior echodense area is not seen consistently, and the inferior effect reported to be haematoma is in a frame where the gain controls have been set too high (the mitral valve leaflets are too bright).

The defect referred to as atrial septal rupture seems clear. However, the defect is quite small and no attempt has been made to quantify it. Even assuming Doppler was unavailable, microbubble contrast material is clearly seen in both illustrations in the right atrium, while none is seen, or commented on, in the left heart (admittedly both being systolic frames). The ease of interatrial shunting (requiring a Valsalva manoeuvre?), colour Doppler, atrial enlargement and clinical assessment of hypoxia (shunt) or pulmonary oedema would help to quantify the significance of the atrial septal defect. It is also of note that the area of the IVC tear, from the central tendon to the right atrium, can be seen transoesophageally with a more inferior and rightward probe position [2].

There is clear evidence of direct trauma to the chest (fractured left clavicle and bilateral pneumothoraces) and there is probably no need to invoke transmitted abdominal pressure as a means of damage. The combination of TOE and TTE, with clinical evidence of bilateral damage, may have suggested an exploratory midline sternotomy rather than thoracotomy. In summary, TOE is a useful emergency investigative tool, but TTE is complementary. In addition, adequate TOE assessment includes not only the diagnosis but an assessment of significance in its clinical setting.

S. J. George
Department of Anaesthesia
St George's Hospital
London

1. Kennedy NJ, Ireland MA, McConaghy PM. Transoesophageal echocardiographic examination of a patient with venacaval and pericardial tears after blunt chest trauma. *British Journal of Anaesthesia* 1995; 75: 495–497.
2. Oka Y, Goldiner PL. *Transoesophageal Echocardiography*. Philadelphia: JB Lippincott & Co, 1992; 55, 237–250.

Sir,—Dr George raises some interesting and worthwhile points. The equipment used was a Toshiba single plane transoesophageal probe with colour Doppler and pulse wave Doppler facility. Transoesophageal echocardiography was carried out in the patient during laparotomy, the patient having presented to the emergency department shocked, with continuing intraperitoneal blood loss. The echodense material anterior to the right atrium and right ventricle may have been blood, but there were no changes to suggest tamponade. Transthoracic echocardiography is certainly a useful adjunct and should generally be performed before transoesophageal echocardiography in all patients, but it was not possible in this patient because of the circumstances of his admission and the haste with which he was transferred to the operating room.

The views presented were chosen because they showed most clearly rupture of the atrial septum. As in any transoesophageal study, additional views, including the standard biatrial view, were obtained, but these did not add specifically to the presentation.

No attempt was made to quantify the defect in the atrial septum; microbubble contrast material was not noted in the left heart. The patient's trachea was intubated and his lungs were ventilated. It is of course useful to do a Valsalva manoeuvre in a conscious patient in a stable condition, but in this case it was not possible.

We agree wholeheartedly that transthoracic echocardiography and transoesophageal echocardiography are complementary, both having specific strengths, adding to the information which may be obtained by either modality alone. There will, however, continue to be patients who, because of their unstable condition, require urgent surgery and in some patients, as in our patient, it will not be possible to perform transthoracic echocardiography.

N. Kennedy
M. Ireland
Shackleton Department of Anaesthetics
Southampton General Hospital
Southampton

British Journal of Anaesthesia 1996; *76*: 338–339

BOOK REVIEWS

Anaesthesia and Critical Care Manual, 2nd Edn. A. J. Cunningham (editor). Published by the Royal College of Surgeons in Ireland. Pp. 244; illustrated. Price IR £15.00.

With the recognition that anaesthetists have an important role in undergraduate education, a second edition of this book has been produced as a basic guide for medical students and newly qualified doctors. It consists of five sections covering preoperative evaluation, intraoperative anaesthetic management, postoperative anaesthetic management, trauma and critical care, and specialized topics including chapters on pancreatitis and chronic pain management. In addition there is a short final section of multiple choice questions on the subjects covered. There is no index, although individual topics are relatively easy to find. Most of the 22 chapters are in the form of "lecture notes" and can be read in less than 15 min, some in considerably less time.

Being a multiauthor book, the chapters vary in style and content, and there is an impression that some may have been edited drastically to reduce the size of the book. Although the information is up to date and presented in a succinct fashion, many chapters can only be regarded as revision notes and barely cover the essentials. For example, the chapter on postoperative pain is three pages long. In contrast, other chapters are excellent synopses of topics undergraduates typically find difficult to understand, in particular the chapter on ARDS. Unfortunately, the text is riddled with spelling mistakes and typographical errors, which at best are annoying and at worst sometimes alter the meaning. There are also notable omissions, the ASA grading system is mentioned in the text, but it is not described. There are many illustrations and photographs but many are far too small to be useful, especially the radiographs. In conclusion, this book will be of little use to anaesthetists in training but may be of some use to medical students and newly qualified doctors as a revision aid.

A. Ogilvy

Anaesthesia and Intensive Care for Patients with Liver Disease. G. R. Park and Y. Kang (editors). Published by Butterworth–Heinemann, Oxford. Pp. 271; indexed; illustrated. Price £75.00.

At first sight this volume appears rather slim, but the 271 pages are densely packed with scientific and clinical information. The editors, recognized as leaders in this area on their respective sides of the Atlantic, have brought together 26 contributors from the UK and the USA. As would be expected, there is a degree of repetition but this does imply that many chapters can be read in isolation. However, I did find that a lack of cross-referencing and an inadequate index made consulting the book for a specific topic difficult.

The book is divided into four sections: assessment, pharmacology, anaesthetic considerations and intensive care. Chapters on paediatrics, acute liver failure and postoperative intensive care are particularly readable and practical. There are detailed and extremely helpful descriptions of liver function tests and coagulation.

Considerable pre-existing knowledge is required for a book such as this, but I did expect more detail on practical techniques, for example intracranial pressure monitoring.

Although the subject matter does not often lend itself to visual presentation, a lack of illustrations gives the text a rather monotonous and dry feel, especially as the print is small. The anatomy section especially would benefit from more illustrations.

These criticisms aside, this is an excellent and comprehensive account. The information is as current as the multiauthor textbook format allows. Although the examination candidate will find too much detail, the chapters I have highlighted provide a good review. The whole book should be available to all anaesthetists and intensivists, wherever they work, as they are increasingly called on to care for patients with liver disease.

I. Wilson

Principles and Practice Series: Respiratory Support. K. Sykes. Published by BMJ Publishing Group, London. Pp. 254; indexed; illustrated. Price £24.95.

This is a splendid little book. Although Keith Sykes complains that he is now a senior citizen with a bus pass, it is only by a lifetime's experience of his subject that so much knowledge can be presented in this concise format. His apologies that brevity has resulted in a didactic style are also unnecessary, as common sense does not need to be long winded.

Within 254 pages there is a broad outline of all aspects of respiratory support from the historical perspective through physiology, mechanics of ventilator modes, artificial airways, clinical indications and general care to advice about sedation. The highlights for me are the 100 pages discussing the physiology and mechanical bases of respiratory support and the subsequent chapters on various means of controlling airway pressure. He makes it all seem simple and easy to understand. It is, however, fair to say that the length of the book implies that certain aspects are a little superficial; for example, ventilator technology is covered in 20 pages with one ventilator chosen to exemplify the important design features of modern machines. I would also have liked a little more about clinical conditions and indications for respiratory support and better integration of the section on choice of support mode for particular clinical conditions, but these caveats do not alter my positive overall impression of the book.

The book is well illustrated with clear line drawings, some of which are old friends from previous Sykes' publications. Each chapter is well referenced with references dating from 1543 to 1994! The text is nicely laid out and appears so crisp and straightforward that it is easy to underestimate just how much information is incorporated into its pages.

Although Keith Sykes has spent his working life deeply engrossed in respiratory physiology, there remains a welcome, honest cynicism about him, for example "there is unfortunately little evidence to indicate that the use of any of the special ventilatory modes has had any influence on mortality" and "if in doubt use a simple ventilator with controlled ventilation; it will probably do less harm in the long term"! I also bond with an author who writes "setting controls poses no problem to the computer literate younger generation but may initially prove time consuming for those used to more conventional control systems".

A recommended snip at £25.

P. G. M. Wallace

The ABC of Resuscitation, 3rd Edn. M. C. Colquhoun, A. J. Handley and T. R. Evans (editors). Published by BMJ Publishing Group, London. Pp. 88; indexed; illustrated. Price £7.95.

Five years after the second edition, this third edition has been completely revised and rewritten by members of the UK Resuscitation Council. There are now 20 chapters, four of which are new, and an extra 18 pages; the chapters on resuscitation in the accident and emergency department and on multiple injured patients have been deleted.

The successful format and style of the previous editions have been retained, with the addition of colour for the algorithms; many black and white photographs complement the text. Up-to-date references are now given at the end of most chapters and equipment manufacturers' addresses listed as appropriate.

The initial chapters cover resuscitation techniques using the European Resuscitation Council (ERC) 1992 guidelines. A new chapter details the management of peri-arrest arrhythmias and the role of the laryngeal mask in the airway at risk is discussed. Resuscitation of infants and children succinctly covers their basic and advanced life support according to 1994 ERC guidelines. There are chapters on resuscitation in pregnancy, at birth, near drowning and the risk of HIV and hepatitis.

The chapter on the ambulance service now includes audit data from the UK and demonstrates the great advances made in the past 5 years; this is followed by a discussion of the role of the general practitioner. There are three chapters on training, including the public, ALS courses, retention of skills and a comprehensive description of adult training manikins. (Alas, the floor space allocated for training areas does not appear to have increased!) The often thorny problems which may arise as the result of a resuscitation attempt are tackled in the chapter on ethics, which stresses the importance of a hospital policy and discusses other areas of concern such as legal aspects, infection hazards and the involvement of relatives. The concluding chapters on drugs and their delivery and cardiac pacing complement the penultimate one on post-resuscitation care.

Editorial mistakes are few but include the 1998 maternal mortality figures, THAN instead of THAM, meq and not mmols, the infant bag valve device without the oxygen reservoir and an obsolescent semi-automatic advisory defibrillator. Although the references are recent, it is a pity that the second edition's further reading section with its many important historic references has been omitted. I find it difficult to reconcile the statement that "cricothyrotomy is contraindicated in children under 12 years of age" with the 1993 ATLS and 1994 PALS teaching, which are in accord with the advice given in the second edition.

This is a very readable book which will appeal to everybody involved in resuscitation, whether at beginner or instructor level, in addition to inspiring an interest in the subject in new readers. The core chapters are carefully structured and develop the most recent ERC guidelines, with the others covering special situations in great detail. There is sufficient information to satisfy the needs of undergraduate and most postgraduate examinations. Armed with this manual, everyone will be able to resuscitate more confidently and competently.

T. M. O'Carroll

ERRATUM

British Journal of Anaesthesia 1995; 75: 588–592

p. 589. In the second paragraph, line 15 should read "This technique is sensitive to 1–2 pg using a *25-μl* sample [13, 14]. A *25-μl* plasma sample is used in the enzyme reaction" and not *25-ml*, as appears in the article.

We apologize to the authors for this confusion.

Papers for publication and all editorial communications should be addressed to:
Professor G. Smith,
Editor, British Journal of Anaesthesia,
University Department of Anaesthesia,
Leicester Royal Infirmary,
Leicester LE1 5WW.
Telephone: 0116 247 0141
Fax: 0116 285 4487

All **business communications** should be sent to the Publishers: Professional & Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR.

The GUIDE TO CONTRIBUTORS may be found in the advertisement section of any issue of the journal (pages ii, iv & vi).

Published monthly. Annual subscriptions: Worldwide £156.00; USA only $245.00 (direct orders only). Trainee rate: Worldwide £75.00. Airmail rates on application. ISSN 0007–0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR. Orders in the USA may be sent to Professional and Scientific Publications, PO Box 408, Franklin, MA 02038, USA.

"WIREX" self-binding cases, which hold a complete volume, i.e. 6 months with room for a supplement and annual handbook, are now available. Price UK £14.00 per two binders, Europe £20.00 per two binders (to cover 1 year). Price includes postage and packing. Rest of the World prices on application. Cheque with order to Hethersett Supplies, Mount Bovers Lane, Hawkwell, Essex SS5 4JA, Tel. (01702) 202393.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statements appear in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statements. Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

© Copyright: 1996 *British Journal of Anaesthesia*
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia*, requests for which should be addressed to the **Publishers**.

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge.

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 76, No. 3 MARCH 1996

EDITORIAL I

Remifentanil—an opioid for the 21st century

Remifentanil is a fentanyl derivative with an ester linkage (3-[4-methoxycarbonyl-4-[(1-oxopropyl) phenylamino]-1-piperidine] propanoic acid, methyl ester). It is a pure μ agonist [1] and the rapid breakdown of the ester linkage by non-specific tissue and plasma esterases is responsible for its unique characteristics. Considerable work is underway investigating this new opioid but, as yet, few data are available in the literature. However, these data enable an initial assessment of the properties of remifentanil and its potential use in anaesthesia.

The speed of onset of action of remifentanil is similar to that of alfentanil [2]. In patients undergoing elective inpatient surgery, the volume of distribution at steady state was 25–40 litre, total clearance 4.2–5 litre min^{-1} and terminal $T_{\frac{1}{2}}$ 10–21 min. Clearance was not affected significantly by body weight, sex or age [3], and it is likely to be independent of renal or hepatic function [4–6]. Furthermore, remifentanil is a poor substrate for butyrylcholinesterases (pseudocholinesterases) *in vitro* and clearance should be unaffected by cholinesterase deficiency or administration of anticholinesterases [data on file, Glaxo].

The main metabolic product of ester hydrolysis is a carboxylic acid derivative (GI90291) which is excreted by the kidneys (elimination half-life 88–137 min [3]). Although elimination of GI90291 is delayed in renal failure [6], significant pharmacological effects are unlikely as its potency relative to remifentanil is only 0.1–0.3%.

At present, remifentanil is formulated in glycine, an inhibitory neurotransmitter. Consequently, spinal or extradural administration is not recommended and there are no data on administration of remifentanil by these routes.

Rapid biotransformation to minimally active metabolites should be associated with a short, predictable duration of action with no accumulation of effect on repeated dosing or with continuous infusion. The available data suggest that remifentanil behaves in this way. Because of its pharmacokinetics, similar properties were expected of alfentanil [7]. However, clinical experience has shown that prolonged infusion of alfentanil may be associated with prolonged recovery time. It is now appreciated that the offset of clinical effect is not simply a function of the half-life, particularly in multicompartmental systems. It may be affected by rate of equilibration between plasma and effector site, method of administration (e.g. continuous infusion, intermittent boluses) and duration of infusion [8, 9]. Hughes, Glass and Jacobs [10] proposed the use of context-sensitive half-time ($T_{\frac{1}{2}\text{context}}$) and defined this as the time for the plasma concentration to decrease by 50% after terminating an i.v. infusion designed to maintain a constant plasma concentration. Context refers to duration of infusion. They demonstrated that context-sensitive half-times of commonly used i.v. anaesthetic agents and opioids could differ markedly from elimination half-lives and were dependent on duration of infusion.

In contrast, because of the unique metabolism of remifentanil, its $T_{\frac{1}{2}\text{context}}$ should be rapid and relatively independent of the duration of infusion. This has been confirmed by *in vivo* studies. Remifentanil $T_{\frac{1}{2}\text{context}}$ was 3.1 min after a 3-h infusion (at a rate sufficient to depress minute ventilation by 40–70%) with a time to pharmacodynamic recovery, as determined by minute ventilation, of 5.8 min. In comparison, the times for alfentanil were 44 and 34.2 min, respectively [11]. In another study, remifentanil and alfentanil were infused i.v. at rates of 0.05 $\mu\text{g kg}^{-1}\,\text{min}^{-1}$ and 0.5 $\mu\text{g kg}^{-1}\,\text{min}^{-1}$, respectively, for 4 h. These infusion rates resulted in a similar degree of respiratory depression. On termination of the infusions, ventilation recovered in 8 min after remifentanil and 61 min after alfentanil [12].

It has been confirmed that the effects of remifentanil are antagonized by naloxone [13]. Its potency is similar to that of fentanyl, and 15–30 times that of alfentanil [14, 15]. The effects of remifentanil on arterial pressure and heart rate after bolus administration of various doses of remifentanil (2–30 $\mu\text{g kg}^{-1}$) have been investigated 10 min after induction of anaesthesia with etomidate and midazolam and maintenance with nitrous oxide–isoflurane–vecuronium [16]. Mean reductions in arterial pressure and heart rate in excess of 20% were found, the effects being unrelated to dose. I.v. administration of remifentanil resulting in hypotension was not associated with histamine release. More detailed haemodynamic investigations are awaited, as are comparisons with other opioids.

The EEG effects of remifentanil are similar to those of other opioids in humans [17] and dogs [18]. Remifentanil infusion is associated with an age-related reduction in the MAC of isoflurane in humans [19]. For example, at age 40 yr, MAC was reduced by 50% at a target remifentanil plasma concentration of 1.2 ng ml^{-1}. The effect was more marked in older patients. A ceiling effect was observed at 32 ng ml^{-1} and MAC was not reduced to zero.

Inevitably, nausea and vomiting may be consequences of remifentanil administration. However, because of its rapid clearance, the incidence of these side effects may prove to be less compared with other opioids in some situations. For example, in patients undergoing unilateral eye surgery under local anaesthesia and i.v. fentanyl or remifentanil, the incidence of nausea after surgery in the recovery room was 54 % and 8 %, respectively [20]. However, it is necessary for these provisional data to be confirmed in larger studies.

The characteristics of a remifentanil–nitrous oxide anaesthetic technique have been reported in the US literature [21–23]. Haemodynamic stability and rapid recovery were described. However, such techniques, without the use of an i.v. or volatile anaesthetic drug, are unlikely to gain widespread acceptance in the UK because of concerns regarding awareness. Studies are underway investigating the use of remifentanil infusions with propofol or volatile anaesthesia but few data are available at present.

Rapid i.v. infusion of large doses of potent opioids are associated with an incidence of muscle rigidity and remifentanil is no exception. In a comparative study of remifentanil 1-μg kg^{-1} bolus followed by 0.5 μg kg^{-1} min^{-1} and alfentanil 25-μg kg^{-1} bolus followed by 1 μg kg^{-1} min^{-1}, the incidence of muscle rigidity was 8 % and 5 %, respectively [data on file, Glaxo]. The majority of cases were described as mild or moderate (i.e. manual ventilation was still possible). As with other opioids, the incidence and severity are dependent on dose and rate of administration.

Based on the evidence so far presented, it may be that remifentanil will be used widely because of its predictability and easily reversible effects. However, its use also presents the anaesthetist with a significant challenge. If remifentanil is the only opioid administered during anaesthesia, it must be remembered that shortly after the end of the procedure, the patient will not benefit from opioid-based analgesia. This problem must be addressed if remifentanil is to be used for procedures associated with significant postoperative pain. Such techniques may include reducing the infusion rate of remifentanil to analgesic doses (which should be relatively simple), immediate administration of longer acting opioids as the effects of remifentanil begin to fade and increased awareness of the possibilities of local anaesthesia.

Such a short-acting and predictable opioid has not been available before to anaesthetists and it is difficult to predict precisely where its niche will lie. However, it has numerous potential applications ranging from short stimulating procedures to prolonged infusions where rapid recovery is required. Possibilities abound, not only in anaesthesia but in intensive care medicine. Overall, it represents a unique alternative to the currently available opioids and the results of further studies are awaited with interest.

J. P. THOMPSON
D. J. ROWBOTHAM
University Department of Anaesthesia
Leicester Royal Infirmary
Leicester LE1 5WW

References

1. James MK, Feldman PL, Schuster SV. Opioid receptor activity of GI87084B, a novel ultra-short acting analgesic in isolated tissues. *Journal of Pharmacology and Experimental Therapeutics* 1991; **259**: 712–718.
2. Glass PSA, Hardman D, Kamiyama Y, Quill TJ, Marton G, Donn KH, Grosse CM, Hermann D. Preliminary pharmacokinetics and pharmacodynamics of an ultra-short acting opioid remifentanil (GI87084B). *Anesthesia and Analgesia* 1993; **77**: 1031–1040.
3. Westmoreland CL, Hoke JF, Sebel PS, Hug CH, Muir KT. Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. *Anesthesiology* 1993; **79**: 893–903.
4. Dershwitz M, Rosow CE, Michalowski P, Connors PM, Hoke JF, Muir KT, Dienstag JL. Pharmacokinetics and pharmacodynamics of remifentanil in volunteer subjects with severe liver disease compared with normal subjects. *Anesthesiology* 1994; **81**: A377.
5. Shlugman D, Dufore S, Dershwitz M, Michalowski P, Hoke J, Muir KT, Rosow C, Glass PSA. Respiratory effects of remifentanil in subjects with severe renal impairment compared to matched controls. *Anesthesiology* 1994; **81**: A1417.
6. Hoke JF, Muir KT, Glass PSA, Shlugman D, Rosow CE, Dershwitz M, Michalowski P. Pharmacokinetics of remifentanil and its metabolite (GR90291) in subjects with renal disease. *Clinical Pharmacology and Therapeutics* 1995; PI–55.
7. Stanski DR, Hug CC. Alfentanil—a kinetically predictable narcotic analgesic. *Anesthesiology* 1982; **57**: 435–438.
8. Shafer SL, Varvel JR. Pharmacokinetics, pharmacodynamics, and rational opioid selection. *Anesthesiology* 1991; **74**: 53–63.
9. Shafer SL, Stanski DR. Improving the clinical utility of anesthetic drug pharmacokinetics. *Anesthesiology* 1992; **76**: 327–330.
10. Hughes MA, Glass PSA, Jacobs JR. Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. *Anesthesiology* 1992; **76**: 334–341.
11. Kapila A, Muir KT, Hermann DJ, Shiraishi M, Leonard MD, Glass PSA. Measured context sensitive half times of remifentanil and alfentanil. *Anesthesiology* 1993; **79**: A377.
12. Glass PSA. Pharmacodynamic comparison of GI87084B, a novel ultra-short acting opioid, and alfentanil. *Anesthesia and Analgesia* 1992; **74**: S113.
13. Amin HM, Sopchak AM, Esposito RN, Graham CL, Batenhorst RL, Camporesi EM. Naloxone reversal of depressed ventilatory response to hypoxia during continuous infusion of remifentanil. *Anesthesiology* 1993; **79**: A1203.
14. Marton JP, Hardmann HD, Kamiyama Y, Donn KH, Glass PSA. Analgesic efficacy of single escalating doses of GI87084B administered intravenously to healthy adult male volunteers. *Anesthesiology* 1991; **75**: A378.
15. Joshi P, Jhaveri R, Bauman V, McNeal S, Batenhorst RL, Glass PSA. Comparative trial of remifentanil and alfentanil for anesthesia induction. *Anesthesiology* 1993; **79**: A379.
16. Sebel PS, Hoke JF, Westmoreland C, Hug CC, Muir KT, Szlam F. Histamine concentrations and haemodynamic responses after remifentanil. *Anesthesia and Analgesia* 1995; **80**: 990–993.
17. Egan TD, Minto C, Lemmens HJM, Muir KT, Hermann DJ, Shafer SL. Remifentanil versus alfentanil: comparative pharmacodynamics. *Anesthesiology* 1994; **81**: A374.
18. Hoffman WE, Cunningham F, James MK, Baughman VL, Albrecht RF. Effects of remifentanil, a new short-acting opioid, on cerebral flow, brain electrical activity, and intracranial pressure in dogs anesthetized with isoflurane and nitrous oxide. *Anesthesiology* 1993; **79**: 107–113.
19. Kapila A, Lang E, Glass P, Sebel P, Shlugman D, Hill A, Wood M, Batenhorst R, Goodman D. MAC reduction of isoflurane by remifentanil. *Anesthesiology* 1994; **81**: A378.
20. Sung YF, Stulting RD, Beatie CD, Stead S, Jamerson BD. Intraocular pressure effects of remifentanil (GI87084B) and alfentanil. *Anesthesiology* 1994; **81**: A36.
21. Kallar SK, Wetchler BV, Shaw DL, Jamerson B. A single blind, comparative study of the safety and efficacy and remifentanil and alfentanil for outpatient anesthesia. *Anesthesiology* 1994; **81**: A32.

22. Dershwitz M, Randel G, Rosow CE, Fragen R, DiBiase PM, Librojo ES, Jamerson B, Shaw DL, Batenhorst R. Dose–response relationship of GI87084B, a new ultra-short acting opioid. *Anesthesiology* 1992; 77: A396.

23. Monk TG, Batenhorst RL, Folger WH, Kirkham AJT, Lemon DJ, Martin KJ, Venker DC. A comparison of remifentanil and alfentanil during nitrous–narcotic anesthesia. *Anesthesia and Analgesia* 1994; 78: S293.

British Journal of Anaesthesia 1996; **76**: 344–346

EDITORIAL II

Voltage-sensitive Ca^{2+} channels and anaesthesia

Many investigators have examined the effects of anaesthetic agents on voltage-sensitive and ligand-gated ion channels and on the regulation of neurotransmitter release in the search for a target site(s) for anaesthesia. However, a single common target remains elusive. Recently, the $GABA_A$ receptor has been championed as a target for all (excluding ketamine) anaesthetic agents. Indeed, several studies have demonstrated that isoflurane exhibits modest but significant stereoselectivity at $GABA_A$ receptors [1–3] but not at L-type voltage-sensitive Ca^{2+} channels [4]. Nevertheless, it is clear that calcium ions (Ca^{2+}) have an important role to play in the mechanism of anaesthesia as this divalent cation contributes to the regulation of neuronal excitability and neurotransmitter release through at least three different types (L, N, P) of voltage-sensitive Ca^{2+} channels [5]. In this editorial we evaluate the evidence in support of voltage-sensitive Ca^{2+} channels as a target for anaesthetic agents.

Since, Nowycky, Fox and Tsien [6] described neuronal voltage-sensitive Ca^{2+}channels as (transient) T-type, (long lasting) L-type and (neither T nor L) N-type, (at least) six different classes of Ca^{2+} channels have now been defined (T, L, N, P, Q and R), both electrophysiologically and pharmacologically [7] (table 1).

T-type

T-type channels are found on both central and peripheral neurones in addition to non-neuronal tissues such as muscle and secretory cells, and are involved in the regulation of burst firing and repetitive discharges as pacemakers in neurones [8]. Although no selective T-channel antagonists have been described, this channel can be distinguished electrophysiologically as the current is low-voltage-activated. This channel may be affected in stroke and seizure as anti-ischaemic agents [8] and anticonvulsants [9, 10] have been reported to reduce the T-current. Electrophysiologically the T-current is inhibited by volatile anaesthetics in a dose-dependent manner [11–13]; pentobarbitone 0.5 mmol $litre^{-1}$ is ineffective [14]. Propofol also depresses this current at high concentrations (0.3 mmol $litre^{-1}$), although an effect at clinically relevant doses has not been demonstrated [15]. It is not clear if the T-channel is involved in the mechanism of general anaesthesia.

L-type

L-type Ca^{2+} channels are located predominantly on neuronal cell bodies, may modify neurotransmitter release under certain circumstances and are involved in some aspects of gene expression [8]. So-called "classic" Ca^{2+} channel blockers inhibit the L-channel; these include dihydropyridines (e.g. nifedipine), phenylalkylamines (e.g. verapamil) and benzothiazepines (e.g. diltiazem). Electrophysiologically the L-current is sensitive to dihydropyridines. Several *in vivo* studies have suggested that the L-channel may contribute to the mechanism of anaesthesia, although blood–brain barrier permeability of L-channel blockers is controversial. Maze, Mason and Kates [16] found a decrease in the MAC for halothane with verapamil in dogs. Moreover, Dolin and Little showed that L-channel blockers such as verapamil, flunarizine and nitrendipine augmented the general anaesthetic potencies of ethanol and pentobarbitone [17], and of benzodiazepines [18], while Bay K8644, an L-channel activator, reduced the anaesthetic actions of benzodiazepines. Consistent with these data, Horvàth, Szikszay and Benedek [19] reported that verapamil enhanced the duration of the hypnotic–anaesthetic action of dexmedetomidine, and that in contrast, Bay K8644 significantly increased the time to onset of hypnosis and attenuated anaesthetic action. In addition to the many reports indicating that both volatile and i.v. anaesthetic agents depress the L-current in skeletal and cardiac muscle [20–23], several reports may be found describing anaesthetic action on L-currents in neuronal tissue; for example depression of neuronal L-channel activity (measured electrophysiologically) [13–15] and binding of L-channel ligands [4, 24].

N-type

N-channels are distributed widely in the nervous system and endocrine cells, and are localized especially on presynaptic terminals of peripheral neurones [25]. N:L channel density ratio in the rat brain is 10–80:1 [26]. N-channels play an important role in the control of neurotransmitter release [27] and are sensitive to ω-conotoxins [8]. To date, there have been few anaesthetic studies performed with N-channels, although volatile anaesthetics have been reported to inhibit unseparated high-voltage-activated currents [11, 12] and dihydropyridine-insensitive neurotransmitter release [25]. Clinically

Table 1 Classification of voltage-sensitive Ca^{2+} channels and the interaction of anaesthetic agents. LVA = Low-voltage activated; HVA = high-voltage activated; NA = not available; DHPs = dihydropyridines; ϖ-CgTx = ϖ-conotoxin GVIA. ↓ = sensitive, → = insensitive, ? = controversial

	Ca^{2+} channel			
	T	L	N	P
Conductance (pS)	8	25	13	14
Activation	LVA	HVA	HVA	HVA
Specific inhibitor	NA	DHPs	ϖ-CgTx	ϖ-Aga-IVA
Volatile anaesthetics	↓	↓	↓	→?
I.v. anaesthetics	↓?	↓	↓	→?

relevant concentrations of isoflurane [13], propofol [15] and several barbiturates [28] significantly depress this current.

P-type

This channel was described initially in cerebellar Purkinje cells [29] and is distributed widely in the central nervous system and surprisingly may constitute about 80% of the voltage-sensitive Ca^{2+} channels in mammalian nerve terminals. This channel may also mediate central synaptic transmission [30–32]. In a study by Hall, Lieb and Franks [33] the P-channel in rat cerebellar Purkinje neurones was found to be insensitive to both volatile and i.v. anaesthetic agents. However, Study [13] showed in rat hippocampal pyramidal neurones that 2.5% isoflurane significantly reduced an ω-conotoxin with nitrendipine-resistant current, which probably includes the P-current.

In the article by Study [13], 2.5% isoflurane was found to inhibit the N- and L-channel peak current by 34 ± 8 and 38 ± 7%, respectively. N- and L-channel sustained currents were decreased by 84 ± 6 and 93 ± 15%, respectively. Gundersen, Umbach and Swartz [28] also reported that pentobarbitone 1 mmol $litre^{-1}$ inhibited 70% of the steady state barium current while the peak inward current was diminished by about 40% through ω-conotoxin-sensitive and dihydropyridine-resistant Ca^{2+} channels in *Xenopus* oocytes. However, the relative importance of peak or sustained current inhibition in the mechanism of anaesthesia needs clarification.

An important consideration in studies of the mechanism of action of anaesthetic agents relates to what is a clinically relevant concentration. In addition, some authors report that brain i.v. anaesthetic concentrations may be significantly different from their plasma concentrations. Archer and colleagues [34] found that the brain concentration of thiopentone was 25% of that of the plasma concentration in rats. In contrast, Shyr and colleagues [35] reported that the brain concentration of propofol after 30 min of i.v. infusion was 7.8 times higher than its plasma concentration in rats.

Another point for consideration is whether or not the *in vitro* IC_{50} value for inhibition of Ca^{2+} channel activity by anaesthetic agents should be related directly to IC_{50} concentrations for general anaesthesia [36], for example MAC. It should be borne in mind that MAC is a whole body-population determination, and it is not known how this relates to 50% inhibition of an electrophysiological–biochemical event in an isolated preparation. Moreover, it is inconceivable that the central nervous system (or cardiovascular system) could withstand a 50% reduction in Ca^{2+} channel activity. Should we be estimating IC_{25}? This seems reasonable as several studies suggest that clinically relevant concentrations of anaesthetics may inhibit release of neurotransmitter with only a 20–30% reduction in Ca^{2+} entry [25, 36, 37].

While a good case can be made for voltage-sensitive Ca^{2+} channels as a target site for anaesthetic agents, further research in this area is essential. Important issues that will need to be addressed using combined physiological, pharmacological and molecular biology approaches include: Is their selectivity in the action of anaesthetic agents for different channel classes? Where on the channel do anaesthetic agents interact? Is there a role for Q, R and other voltage-sensitive Ca^{2+} channels in anaesthesia? Only when this information is gathered will it be possible to fully confirm or exclude a role for this important class of ion channels in the process of anaesthesia.

K. HIROTA
D. G. LAMBERT
University Department of Anaesthesia
Leicester Royal Infirmary
Leicester LE1 5WW

References

1. Moody EJ, Harris BD, Skolnick P. Stereospecific actions of the inhalation anesthetic isoflurane at the $GABA_A$ receptor complex. *Brain Research* 1993; **615**: 101–106.
2. Jones MV, Harrison NL. Effects of volatile anesthetics on the kinetics of inhibitory postsynaptic currents in cultured rat hippocampal neurons. *Journal of Neurophysiology* 1993; **70**: 628–632.
3. Harris BD, Moody EJ, Basile A, Skolnick P. Volatile anesthetics bidirectionally and stereospecifically modulate ligand binding at $GABA_A$ receptors. *European Journal of Pharmacology* 1994; **267**: 269–274.
4. Moody EJ, Harris B, Hoehner P, Skolnick P. Inhibition of [^{3}H]isradipine binding to L-type calcium channels by the optical isomers of isoflurane. *Anesthesiology* 1994; **81**: 124–128.
5. Takahashi T, Momiyama A. Different types of calcium channels mediate central synaptic transmission. *Nature (London)* 1993; **366**: 156–158.
6. Nowycky MC, Fox AP, Tsien RW. Three types of neuronal calcium channels with different calcium agonist sensitivity. *Nature (London)* 1985; **316**: 440–443.
7. Godfraid T, Govoni S. Recent advances in the pharmacology of Ca^{2+} and K^+ channels. *Trends in Pharmacological Sciences* 1995; **16**: 1–4.
8. Spedding M, Lepagnol J. Pharmacology of sodium and calcium channel modulation in neurons: implications for neuroprotection. *Biochemical Society Transactions* 1995; **23**: 633–636.
9. Coulter DA, Hunguenard JR, Prince DA. Specific petit mal anticonvulsants reduce calcium currents in thalamic neurones. *Neuroscience Letters* 1989; **98**: 74–78.
10. Yaari Y, Hamon B, Lux HD. Development of two types of calcium channels in cultured mammalian hippocampal neurons. *Science* 1987; **235**: 680–682.
11. Takenoshita M, Steinbach JH. Halothane blocks low-voltage-activated calcium current in rat sensory neurons. *Journal of Neuroscience* 1991; **11**: 1404–1412.
12. Herrington J, Stern RC, Evers AS, Lingle CJ. Halothane inhibits two components of calcium current in clonal (GH_3) pituitary cells. *Journal of Neuroscience* 1991; **11**: 2226–2240.
13. Study RE. Isoflurane inhibits multiple voltage-gated calcium currents in hippocampal pyramidal neurons. *Anesthesiology* 1994; **81**: 104–116.
14. Gross RA, Macdonald RL. Differential actions of pentobarbitone on calcium current component of mouse sensory neurones in culture. *Journal of Physiology (London)* 1988; **405**: 187–203.
15. Olcese R, Usai C, Maestrone E, Nobile M. The general anesthetic propofol inhibits transmembrane calcium current in chick sensory neurons. *Anesthesia and Analgesia* 1994; **78**: 955–960.
16. Maze M, Mason DM, Kates RE. Verapamil decreases MAC for halothane in dogs. *Anesthesiology* 1983; **59**: 327–329.
17. Dolin SJ, Little HJ. Augmentation by calcium channel antagonists of general anaesthetic potency in mice. *British Journal of Pharmacology* 1988; **88**: 909–914.

18. Dolin SJ, Patch TL, Rabbani M, Taberner PV, Little HJ. Differential interactions between benzodiazepines and the dihydropyridines, nitrendipine and Bay K 8644. *Neuropharmacology* 1991; **30**: 217–224.
19. Horvàth G, Szikszay M, Benedek G. Calcium channels are involved in the hypnotic–anesthetic action of dexmedetomidine in rats. *Anesthesia and Analgesia* 1992; **74**: 884–888.
20. Terrar DA. Structure and function of calcium channels and the actions of anaesthetics. *British Journal of Anaesthesia* 1993; **71**: 39–46.
21. Eskinder H, Rusch NJ, Supan FD, Kampine JP, Bosnjak ZJ. The effects of volatile anesthetics on L- and T-type calcium channel currents in canine cardiac purkinje cells. *Anesthesiology* 1991; **74**: 919–926.
22. Louis CF, Roghair T, Mickelson JR. Volatile anesthetics inhibit dihydropyridine binding to malignant hyperthermia-susceptible and normal pig skeletal muscle membranes. *Anesthesiology* 1994; **80**: 618–624.
23. Fruen BR, Mickelson JR, Roghair T, Litterer LA, Louis CF. Effects of propofol on Ca^{2+} regulation by malignant hyperthermia-susceptible muscle membranes. *Anesthesiology* 1995; **82**: 1274–1282.
24. Drenger B, Heitmiller ES, Quigg M, Blank TJJ. Depression of calcium channel blocker binding to rat brain membranes by halothane. *Anesthesia and Analgesia* 1992; **74**: 758–761.
25. Kress HG, Tas PWL. Effects of volatile anaesthetics on second messenger Ca^{2+} in neurones and non-muscular cells. *British Journal of Anaesthesia* 1993; **71**: 47–58.
26. Wagner JA, Snowman AM, Biswas A, Olivera BM, Snyder SH. ϖ-Conotoxin GVIA binding to a high-affinity receptor in brain: characterization, calcium sensitivity, and solubilization. *Journal of Neuroscience* 1988; **8**: 3354–3359.
27. Wheeler DB, Randall A, Tsien RW. Roles of N-type and Q-type Ca^{2+} channels in supporting hippocampal synaptic transmission. *Science* 1994; **264**: 107–111.
28. Gundersen CB, Umbach JA, Swartz BE. Barbiturates depress currents through human brain calcium channels studied in *Xenopus* oocytes. *Journal of Pharmacology and Experimental Therapeutics* 1988; **247**: 824–829.
29. Llinàs R, Sugimori M, Lin JW, Cherksey B. Blocking and isolation of a calcium channel from neurons in mammals and cephalopods utilizing a toxin fraction (FTX) from funnel-web spider poison. *Proceedings of the National Academy of Sciences USA* 1989; **86**: 1689–1693.
30. Llinàs R, Sugimori M, Hillman DE, Cherksey B. Distribution and functional significance of the P-type, voltage-dependent Ca^{2+} channels in the mammalian central nervous system. *Trends in Neuroscience* 1992; **15**: 351–355.
31. Uchitel OD, Protti DA, Sanchez V, Cherksey B, Sugimori M, Llinàs R. P-type voltage-dependent calcium channel mediates presynaptic calcium influx and transmitter release in mammalian synapses. *Proceedings of the National Academy of Sciences USA* 1992; **89**: 3330–3333.
32. Mintz IM, Venema VJ, Swiderek KM, Lee TD, Bean BP, Adams ME. P-type calcium channels blocked by the spider toxin ϖ-Aga-IVA. *Nature (London)* 1992; **355**: 827–829.
33. Hall C, Lieb WR, Franks NP. Insensitivity of P-type calcium channels to inhalational and intravenous general anesthetics. *Anesthesiology* 1994; **81**: 117–123.
34. Archer DP, Ewen A, Roth SH, Samanani N. Plasma, brain and spinal cord concentration of thiopental associated with hyperalgesia in the rat. *Anesthesiology* 1994; **80**: 168–176.
35. Shyr MH, Tsai TH, Tan PPC, Chen CF, Chan SHH. Concentration and regional distribution of propofol in brain and spinal cord during propofol anaesthesia in the rat. *Neuroscience Letters* 1995; **184**: 212–215.
36. Frank NP, Lieb WR. Molecular and cellular mechanisms of general anaesthesia. *Nature (London)* 1994; **367**: 607–614.
37. Miao N, Frazer MJ, Lynch C III. Volatile anesthetics depress Ca^{2+} transients and glutamate release in isolated cerebral synaptosomes. *Anesthesiology* 1995; **83**: 593–603.

British Journal of Anaesthesia 1996; **76**: 347–351

CLINICAL INVESTIGATIONS

Prediction of postoperative nausea and vomiting using a logistic regression model†

C. C. Toner, C. J. Broomhead, I. H. Littlejohn, G. S. Samra, J. G. Powney,
M. G. A. Palazzo, S. J. W. Evans and L. Strunin

Summary

In a previous study, logistic regression analysis was used to determine the association of independent fixed patient factors with the incidence of postoperative nausea and vomiting (PONV). Female sex, previous history of PONV, use of postoperative opioids, previous history of motion sickness and an interaction between male sex and previous history of PONV were combined in an equation from which risk of PONV could be estimated. The present study was designed to test this equation in a group of patients with wide selection criteria. Data on 400 patients were collected in relation to pre-, per- and postoperative factors which may influence the incidence of PONV. The equation was used to predict PONV, and actual outcome was compared with that predicted. The overall incidence of PONV was 36%. The equation predicted an overall probability of PONV of 27.4%. If the model was used to define individual patients as predicted to have or not to have PONV, it was correct only 71% of the time. However, there was good agreement between the actual incidences of PONV and those predicted among the 16 risk groups created by the model. (*Br. J. Anaesth.* 1996; **76**: 347–351)

Key words
Vomiting, nausea. Vomiting, incidence. Vomiting, nausea, anaesthetic factors. Vomiting, nausea, surgical factors. Model, logistic regression.

The incidence of postoperative nausea and vomiting (PONV) has remained nearly constant over the past 30 yr (20–30%) despite considerable changes in other aspects of anaesthetic practice [1–11]. Until recently, PONV was considered a relatively unimportant postoperative complication, but the growing emphasis on day-case surgery has focused attention on complications which might delay discharge. Development of effective antiemetic therapy has been hampered by the multifactorial nature of PONV. This has presented considerable difficulty to investigators in ensuring adequate standardization of study groups for the risk of PONV. A more rigorous approach to the study of PONV requires quantification of the relative contribution of individual patient, surgical and anaesthetic factors in its aetiology. This information could be used to ensure that drug treated and control groups of patients are at equal risk of PONV before operation. It would also allow comparison of observed and predicted outcomes between studies.

In a preliminary study, Palazzo and Evans [12] developed a model for prediction of postoperative emesis in patients undergoing minor orthopaedic surgery. Variable factors (i.e. those that may be modified by the anaesthetist) were controlled. This involved a standardized anaesthetic technique of induction with thiopentone 4 mg kg^{-1} followed by spontaneous ventilation with a mixture of 2% enflurane and 65% nitrous oxide in oxygen. Fixed patient factors were allowed to be distributed freely (e.g. age, weight, sex). Logistic regression analysis was used to determine the association of independent fixed patient factors with the incidence of PONV. The fixed patient factors of sex, history of previous emesis, postoperative opioids and an interaction between sex and previous emetic history were identified as significant independent variables. Motion sickness had a weak association which did not reach statistical significance but was retained in the model on the basis that this was probably a result of the small number of patients. These factors were expressed in a logistic regression equation from which the risk of postoperative emesis for an individual patient could be calculated before operation. The object of the current study was to test the predictive value of this model in a heterogeneous patient group where surgical and anaesthetic factors were subject to considerable variation.

Patients and methods

After obtaining approval from the hospital Ethics Committee, we studied 400 patients (274 female). Twenty-one patients were undergoing elective ENT

Christopher C. Toner, bm, frca, Christopher J. Broomhead, mb, bs, frca, Ian H. Littlejohn, mb, bs, frca, Gurdip S. Samra, mb, bs, bsc, frca, Jolyon G. Powney, mb, bs, bsc, da, frca, Mark G. A. Palazzo, mb, chb, frcp, frca, md, Leo Strunin, md, frca, frcpc (Anaesthetics Unit); Stephen J. W. Evans, msc (Department of Epidemiology and Medical Statistics); London Hospital Medical College, University of London, The Royal London Hospital, Whitechapel, London E1 1BB. Accepted for publication: October 10, 1995.

† Presented in part at the Anaesthetic Research Society London Meeting, November 19–20, 1993 (*British Journal of Anaesthesia* 1994; 72: 488P).

Table 1 Factors recorded in the questionnaire

Preoperative	Peroperative	Postoperative
Name	Duration of fast	Position in post-anaesthetic recovery room
Age	Anaesthetist	Time of first oral intake
Hospital no.	Surgeon	Opioid analgesia
ASA physical status score	Operation	Antiemetics
Ethnic origin	Duration of operation	Nausea or vomiting during first 24 h
Sex	Induction agent	
Previous anaesthetics	Neuromuscular blocker	
Previous postoperative nausea and vomiting	Opioid	
	Antiemetic	
History of motion sickness	Gases/vapours	
History of vertigo	Other drugs	
History of migraine headaches	Airway: use of tracheal tube, laryngeal mask airway, oropharyngeal airway, etc	
History of morning sickness		
History of starvation nausea		
Smoking	IPPV/SV	
Allergies	Antagonism of neuromuscular block	
Medication	I.v. fluids	
Medical problems	Lowest systolic arterial pressure	
	Lowest Sa_{O_2}	
	Highest E'_{CO_2}	

Table 2 Actual *vs* predicted PONV

	Actual non-vomiter	Actual vomiter	Total
Predicted non-vomiter	226	85	311
Predicted vomiter	31	58	89
Total	257 (64.2%)	143 (35.8%)	400 (100%)

surgery, 35 maxillofacial surgery, 49 orthopaedic surgery, 141 gynaecological surgery, 114 general surgery and 22 urological surgery. For 18 patients the surgical specialty was not recorded. Median age was 44 (range 17–91) yr and ASA status was I–III (I 63%; II 29%; III 8%). The patients were interviewed the night before surgery and 24 h after operation. A questionnaire was completed which included both fixed and variable patient factors which previous studies have suggested influence PONV (table 1) [13]. In this study, variable factors relating to the perioperative period were not controlled. Details from the intraoperative and early recovery periods were recorded by the patient's anaesthetist and recovery nurse. All patients were allowed opioid analgesics and antiemetics as required after operation. Twenty four hours later the patient was revisited by an investigator and episodes of PONV, time of first oral intake, and use of opioids and antiemetics were recorded. Postoperative emesis was defined as vomiting (an integrated reflex resulting in expulsion of gastric contents), retching (a non-productive vomit) or nausea (the sensation of wishing to vomit).

Multiple linear regression allows the prediction of a single dependent variable (outcome) from the values of other explanatory (predictor) variables. However, this approach is only suitable when the outcome variable is continuous (e.g. birth weight). When the outcome variable is binary, as in the present study, multiple logistic regression is used [14]. To avoid impossible values of the dependent variable, a logit transformation is performed. If P is the probability an individual will vomit, then $1-P$ is the probability they will not. The ratio $P/1-P$ is termed the odds and thus the log odds is

$$\text{logit}(P) = \ln(P/1-P)$$

The relative effects of the fixed patient factors identified by Palazzo and Evans [12] were summarized in the equation:

$$\text{log odds (of emesis)} = -5.03+2.24\ \text{(opioid analgesics)}+3.97\ \text{(previous emetic history)}+2.4\ \text{(sex)}+0.78\ \text{(motion sickness)}-3.2\ \text{(sex}\times\text{previous emetic history)}.$$

To calculate the predicted probability of postoperative emesis for each patient, the use of opioid analgesics in the first 24 h after operation, previous postoperative emetic history, previous history of motion sickness or female sex was coded as 1, while absence of a factor or male sex was coded as 0. For example, from this formula a male with a previous history of emesis, motion sickness and who also received opioids would have a log odds of emesis in the first 24 h after operation of 1.96. This results in a calculated probability of emesis of 0.876 or 87.6%. For calculating the risk of any group of patients, the individual patient probabilities should be summed and divided by the number of patients to provide a mean (SD). Each of the four factors used in this equation has just two possible values so that there are $2^4 = 16$ risk groups. Each group has a different predicted probability of PONV ranging from males with none of the risk factors with a predicted probability of PONV of 0.6%, to the group used as an example above with all of the risk factors for whom the predicted risk is 88%.

When predicting outcome for individuals, the logical cut-off is 50%. Those with a predicted probability of less than 50% become predicted non-vomiters and those with a predicted probability of 50% or greater predicted vomiters.

The association of the factors recorded in the questionnaire (table 1) with PONV was assessed in the current study group. Nominal data were explored initially by univariate analysis with contingency tables between vomiters and non-vomiters and continuous variables by logistic regression. The combined effects of all variables were then analysed by stepwise logistic regression. The statistical software used was STATA (Stata Inc. College Station, TX 77840, USA).

Results

Of the 400 patients included in the study, the model had an average predicted probability of PONV of 27.4%. The number who did have PONV was 143 (36%). When a 50% cut-off was used to predict which individuals would or would not have PONV, the model predicted that 89 (22%) would vomit (table 2). Of these, 58 did vomit giving the model a positive predictive value of 65%. A total of 311 patients were predicted not to vomit and this proved to be the case in 226, producing a negative predictive value of 73%. The overall correct prediction rate of the model was 71%. A total of 143 patients vomited and the model correctly predicted 58 of these, giving a sensitivity of 41%; 257 patients did not vomit and the model correctly predicted 226 of these, giving a specificity of 88%.

Table 3 shows the predicted and actual outcomes for each of the 16 risk groups generated by the model. In general, there was better agreement in the groups that were larger or at higher predicted risk of PONV. This became more apparent when the predicted percentage in each of the 16 groups was plotted against the actual percentage of PONV (fig. 1). In figure 1, the groups are shown as circles, the radius of which is proportional to the size of that group. The overall incidence of PONV was higher than that predicted and this is reflected in figure 1 where most of the circles lie just above the line that would represent perfect prediction by the model. The agreement between the observed and predicted rate of PONV was much greater than would be expected by chance (correlation weighted by group size = 0.89, $P < 0.005$).

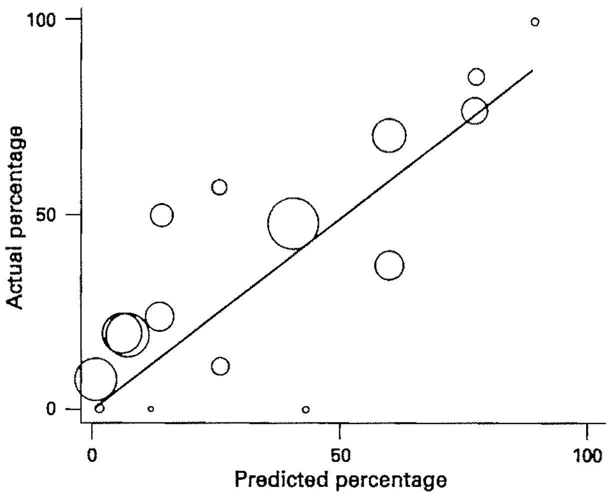


Figure 1 Actual *vs* predicted percentage of PONV. Each group is represented by a circle of radius proportional to the number of subjects in the group.

In this study, factors that were significantly more prevalent in vomiters than non-vomiters were female sex, previous history of postoperative emesis, increased duration of anaesthesia and use of the laryngeal mask airway, opioids or any neuromuscular blocking agent. Factors that were not significantly different for vomiters or non-vomiters were age, ASA status, ethnic origin, previous history of morning sickness, motion sickness, vertigo, migraine headache or starvation nausea, smoking, type of premedication, preoperative or intraoperative use of antiemetics, grade of anaesthetist, nature of surgery, induction agent, volatile agent, use of a tracheal tube, positive pressure ventilation, lowest recorded intraoperative systolic arterial pressure or arterial oxygen saturation, or highest end-tidal carbon dioxide. The combined effects of all variables were then analysed by stepwise logistic regression. Three factors were independent contributors to PONV. These were sex (odds ratio 2.9), previous emetic history (odds ratio 2.9) and opioid analgesics (odds ratio 3.7). All of these were highly statistically significant ($P < 0.0005$). As in the original study, motion

Table 3 Predicted and actual outcomes for the 16 patient risk groups

Sex (female = 1)	Previous PONV	Motion sickness	Opioids	No. of subjects	Predicted % of PONV	Actual % of PONV	Predicted no. of vomiters	Actual no. of vomiters
0	0	0	0	53	0.65	7.54	0.34	4
0	0	1	0	2	1.41	0	0.028	0
0	0	0	1	51	5.79	19.60	2.95	10
1	0	0	0	63	6.72	19.05	4.24	12
0	0	1	1	1	11.82	0	0.12	0
1	1	0	0	25	13.47	24	3.37	6
1	0	1	0	16	13.59	50	2.17	8
1	1	1	0	7	25.35	57.14	1.78	4
0	1	0	0	9	25.73	11.11	2.32	1
1	0	0	1	83	40.37	48.19	33.51	40
0	1	1	0	1	43.05	0	0.43	0
1	1	0	1	34	59.39	70.59	20.19	24
1	0	1	1	24	59.63	37.5	14.31	9
1	1	1	1	22	76.13	77.27	16.75	17
0	1	0	1	7	76.49	85.71	5.36	6
0	1	1	1	2	87.65	100	1.75	2

sickness narrowly failed to reach statistical significance.

Discussion

An effective model for estimation of the risk of PONV using fixed patient factors would be a potentially useful tool for future investigators in ensuring that their study groups are balanced. The model described in this article had been developed intentionally in a restricted patient group that received a standardized anaesthetic technique to maximize the relative effects of fixed patient factors [12]. The current study tested this model in a larger and heterogeneous patient group.

There are different approaches which may be used to assess the performance of the model. If individual patients are defined as predicted vomiters or non-vomiters, then a predicted risk of 50% is a logical cut-off. This resulted in a correct prediction rate of 71% which although reasonable, is in fact not substantially greater than chance alone would allow. While this indicates that the model is not outstanding at predicting outcomes for individual patients, this approach tends to underestimate the predictive value of the model because it does not demonstrate how it performs within groups of patients. Many patients will have a predicted risk of PONV of the order of 50%. With a 50%, yes/no cut-off, the model will often appear wrong because by definition the patient has only a 50:50 chance of PONV. If the model is effective at determining risk of PONV, then the actual incidence of PONV in groups of patients with the same combination of factors will be similar to that predicted. This was indeed the case in the larger groups of patients and those at greater risk of PONV (fig. 1, table 3). This is seen best in the 22 patients predicted to have a 76% risk of PONV and among whom the actual incidence was 77%. The agreement between the observed and predicted rate of PONV was much greater than would be expected by chance (correlation weighted by group size = 0.89, $P < 0.005$). Thus the model is effective at estimating the risk of PONV in groups of patients and particularly those at high risk of PONV. This is exactly the group that investigators should be targeting, both because they represent a group most likely to benefit from improved antiemetic therapy and because use of a high-risk group increases the power of the study.

The study also confirmed that among fixed patient factors, female sex, use of opioids and previous history of PONV contribute disproportionately to subsequent episodes. Of these, previous history of PONV is often overlooked in study standardization. The contribution of female sex as a fixed patient factor in PONV has been noted by many previous investigators, although restricted to adult, premenopausal women. This predisposition extends to types of surgery not normally associated with a high incidence of PONV (e.g. orthopaedic surgery [9]). These observations suggest that fluctuations in female sex hormones during the menstrual cycle play an important role and indeed the greatest incidence of PONV in adult females occurs during the third and fourth week of the menstrual cycle [15].

Nausea and vomiting are common side effects of perioperative opioids, irrespective of the route of administration. There is evidence that the emetic effects of opioids are mediated via opioid receptors in the area postrema, resulting in activation of the vomiting centre. It has also been speculated that by directly activating the vestibular system, opioids increase the sensitivity of the emetic reflex [16].

The association of previous history of PONV with subsequent episodes has received far less attention, although as long ago as 1964 Purkiss observed a three-fold increase in vomiting in the first 24 h in patients who had experienced previous postoperative vomiting [17]. It has been suggested that those individuals with previous PONV or motion sickness may have a well developed reflex arc for vomiting [18].

The impact of a significant improvement in antiemetic therapy would be considerable, particularly at a time when there is increasing emphasis on early hospital discharge. Unfortunately, the difficulties of adequately standardizing patient groups for this highly multifactorial complaint have limited the validity of much of the work in this area. This study confirms that in a large and heterogeneous patient group, female sex, use of opioids and previous history of PONV play a substantial part in determining subsequent episodes of PONV. A model based on these factors and motion sickness was not particularly effective when used to define patients simply as predicted to have or not to have PONV. However, in predicting the risk of PONV in groups of patients with various combinations of risk factors, the model was effective, with good agreement between observed and predicted incidences. This was most significant in larger groups or those at greater risk of PONV.

References

1. Waters RM. The present state of cyclopropane. *British Medical Journal* 1936; 2: 1013–1017.
2. Dent S, Ramachandra V, Stephen CR. Postoperative vomiting; incidence analysis and therapeutic measures in 3000 patients. *Anesthesiology* 1955; 16: 564–572.
3. Burtles R, Peckett BW. Postoperative vomiting. *British Journal of Anaesthesia* 1957; 29: 114–123.
4. Bonica JJ, Crepps W, Monk B, Bennett B. Postoperative nausea, retching and vomiting. *Anesthesiology* 1958; 19: 532–540.
5. Bellville JW, Bross IDJ, Howlands WS. Postoperative nausea and vomiting. IV, Factors related to postoperative nausea and vomiting. *Anesthesiology* 1960; 21: 186–193.
6. Adriani J, Summers FW, Anthony SO. Is prophylactic use of antiemetics in surgical patients justified? *Journal of the American Medical Association* 1961; 175: 666–671.
7. McKie BD. Postoperative nausea and vomiting: A review of their incidence, causes and effects. *Australian and New Zealand Journal of Surgery* 1970; 39: 311–314.
8. Kortilla K, Kauste A, Auvinen J. Comparison of domperidone, droperidol and metoclopramide in the prevention and treatment of nausea and vomiting after balanced general anesthesia. *Anesthesia and Analgesia* 1979; 58: 396–400.
9. Mortensen PT. Droperidol: postoperative antiemetic effect when given intravenously to gynaecological patients. *Acta Anaesthesiologica Scandinavica* 1982; 26: 48–52.

10. Gold BS, Kitz DS, Lecky JH, Heuhaus JM. Unanticipated admission to hospital following ambulatory surgery. *Journal of the American Medical Association* 1989; **262**: 3008–3010.
11. Patel RI, Hannallah RS. Anesthetic complications following pediatric ambulatory surgery: A 3-yr study. *Anesthesiology* 1988; **69**: 1009–1012.
12. Palazzo M, Evans R. Logistic regression analysis of fixed patient factors for postoperative sickness: a model for risk assessment. *British Journal of Anaesthesia* 1993; **70**: 135–140.
13. Watcha MF, White PF. Postoperative nausea and vomiting. *Anesthesiology* 1992; **77**: 162–184.
14. Altman D. *Practical Statistics for Medical Research.* London: Chapman and Hall, 1991.
15. Bellville JW. Postanesthetic nausea and vomiting. *Anesthesiology* 1961; **21**: 773–780.
16. Andrews PLR. Physiology of nausea and vomiting. *British Journal of Anaesthesia* 1992; **69** (Suppl. 1): 2–19S.
17. Purkiss IE. Factors that influence postoperative vomiting. *Canadian Anaesthetists Society Journal* 1964; **11**: 335–353.
18. Palazzo MGA, Strunin L. Anaesthesia and emesis: I. Etiology. *Canadian Anaesthetists Society Journal* 1984; **31**: 178–187.

British Journal of Anaesthesia 1996; 76: 352–357

Metabolic and hormonal responses to induced hypotension for middle ear surgery

M. C. NEWTON, G. D. CHADD, B. O'DONOGHUE, S. M. SAPSED-BYRNE AND G. M. HALL

Summary

We have investigated in 30 patients the metabolic and hormonal responses to middle ear surgery using induced hypotension to a mean arterial pressure of 55 mm Hg. A standardized anaesthetic technique of propranolol, thiopentone–vecuronium–isoflurane was used in all patients and hypotension induced with sodium nitroprusside, trimetaphan camsylate or additional isoflurane. All patients showed a classic stress response with an increase in circulating blood glucose, cortisol and growth hormone concentrations. Blood lactate and plasma uric acid concentrations changed little during operation, suggesting that tissue oxygenation was adequate. However, the former declined after operation, possibly as a result of the concomitant use of propranolol. There were no significant differences between the three hypotensive techniques in their effects on the hormonal and metabolic response, although the increase in blood glucose concentration in the trimetaphan group was obtunded. We conclude that induced hypotension for middle ear surgery induced an endocrine and metabolic response of small magnitude and short duration. (*Br. J. Anaesth.* 1996; **76**: 352–357)

Key words

Anaesthetic techniques, hypotensive. Metabolism, glucose. Hormones, glucocorticoid. Surgery, otolaryngological.

The classic endocrine and metabolic response to surgery is approximately proportional to the severity of the surgical trauma. For example, cardiac surgery results in large and sustained changes in catabolic hormone secretion with prolonged hyperglycaemia, whereas cataract extraction evokes only transient increases in circulating cortisol and glucose concentrations [1]. Hormonal responses to the use of induced hypotension for surgery have received considerable attention, but have been confined mostly to investigation of changes in sympathoadrenal activity and in the renin–angiotensin–aldosterone axis [2–4]. Although Engquist and colleagues examined the glucose and cortisol response to middle ear surgery in six patients, it is not clear if induced hypotension was used [5].

The aim of the present study was to compare the effects of three hypotensive regimens, isoflurane, sodium nitroprusside and trimetaphan camsylate, on the metabolic and endocrine responses to middle ear surgery conducted at a mean arterial pressure (MAP) of 55 mm Hg. The use of nitroprusside compared with trimetaphan is associated with an increase in sympathoadrenal activity [2] and would be expected to stimulate glucose and lipid metabolism. However, it is usual practice to administer a β adrenergic blocking drug to prevent reflex tachycardia after induced hypotension and it is not known if the use of such an agent may modify the metabolic response.

Patients and methods

After obtaining approval from the Ethics Committee of the Royal National Throat, Nose and Ear Hospital and written, informed consent, 30 ASA I patients undergoing middle ear surgery were allocated randomly to receive isoflurane, sodium nitroprusside or trimetaphan camsylate to induce hypotension.

Patients were premedicated with papaveretum 0.3 mg kg^{-1} and hyoscine 0.006 mg kg^{-1} i.m., approximately 1.5 h before induction of anaesthesia. On arrival in the anaesthetic room, a radial artery cannula was inserted for measurement of arterial pressure and a central vein catheterized for administration of fluids. Routine monitoring commenced. After a rest period of at least 10 min, a control arterial sample was collected for measurement of metabolite and hormone concentrations.

Propranolol was given slowly i.v. to a total dose of 0.05 mg kg^{-1}, or was discontinued if heart rate slowed to 50 beat min^{-1} or less (seven patients in each group received the total dose). Five minutes later anaesthesia was induced with thiopentone and tracheal intubation facilitated with vecuronium 0.1 mg kg^{-1}. The lungs were ventilated with isoflurane and 50 % nitrous oxide in oxygen and the end-tidal partial pressure of carbon dioxide was maintained at 3.5 kPa. The patient was transferred to theatre and positioned on the table with an 8°

M. C. NEWTON, MB, BS, FRCA, G. D. CHADD, MB, CHB, FFARCSI, B. O'DONOGHUE, MD, FRCA, Department of Anaesthesia, Royal National Throat, Nose and Ear Hospital, Gray's Inn Road, London WC1X 8DA. S. M. SAPSED-BYRNE, BSC, Department of Anaesthesia, Hammersmith Hospital, Royal Postgraduate Medical School, London W12 0HS. G. M. HALL, MB, BS, PHD, FIBIOL, FRCA, Department of Anaesthesia, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE. Accepted for publication: October 29, 1995.

Correspondence to G.M.H.

head-up tilt. Measurement of arterial pressure continued with the transducer placed at the mid-axillary line. Anaesthesia was maintained with isoflurane at an end-tidal concentration of 0.8%. Sodium chloride solution (0.9%) was infused i.v. at 5 ml kg^{-1} h^{-1} during surgery and at 3 ml kg^{-1} h^{-1} in the postoperative period.

Hypotension was induced before surgery with the aim of achieving and maintaining MAP at 55 mm Hg throughout surgery. Patients allocated to the isoflurane group received as much isoflurane as necessary to maintain this MAP. Patients in the remaining two groups continued with isoflurane at an end-tidal concentration of 0.8%. In the trimetaphan group, MAP was controlled with an infusion of trimetaphan camsylate (500 mg in 0.9% sodium chloride solution 490 ml) and the nitroprusside group by an infusion of sodium nitroprusside (50 mg in 5% glucose 2 ml and 0.9% sodium chloride solution 498 ml). The hypotensive drugs were given via a separate i.v. cannula. Any increase in MAP in response to surgical stimulation was treated by increasing the dose of the appropriate hypotensive agent. Neuromuscular block was maintained with an infusion of vecuronium.

Twenty and 40 min after the start of surgery, additional arterial samples were collected for measurement of hormone and metabolite concentrations. Towards the end of surgery the hypotensive agent was withdrawn to permit MAP to return to normal and haemostasis obtained. Papaveretum 0.2 mg kg^{-1} and prochlorperazine 0.15 mg kg^{-1} were given i.m. Residual neuromuscular block was antagonized by neostigmine and glycopyrronium. Haemodynamic monitoring was maintained for at least 2 h after completion of surgery and additional arterial samples collected 30, 60 and 120 min after normotension had been achieved. Glycopyrronium was given i.v. if heart rate was less than 50 beat min^{-1}.

METABOLITE AND HORMONE ANALYSIS

Blood glucose, lactate and pyruvate concentrations and plasma non-esterified fatty acid (NEFA) concentrations were determined enzymatically by standard methods [6]. Plasma uric acid values were measured colorimetrically using the enzyme uricase [7]. Serum cortisol, growth hormone (GH) and insulin concentrations were measured with sensitive and specific radioimmunoassays that have been described in detail previously [8]. The intra- and inter-assay coefficients of variation were 4.3% and 7.0% for cortisol, 8.2% and 10.0% for GH, and 6.6% and 9.5% for insulin, respectively. Packed cell volume (PCV) was measuring using the microcapillary method.

STATISTICAL ANALYSES

Parametric data are expressed as mean (SEM) and analysed using two-way analysis of variance (ANOVA), with Dunnett's test for within-group changes with respect to the control sample. Between-group changes were analysed by ANOVA. GH data were not normally distributed and therefore expressed as median (range). Within-group analysis was made with Friedman's two-way analysis of variance and between-group comparisons with the Kruskal–Wallis test. $P < 0.05$ was accepted as significant.

Results

Two of the 30 patients studied had abnormally increased fasting blood glucose concentrations and data from these patients were excluded. There were no significant differences between the three groups in age, sex distribution, body weight, body mass index, time of surgery, type of surgery, duration of preoperative starvation, dose of propranolol and duration of hypotension (table 1). The surgeons noted no difference in the quality of the operative field for the three hypotensive regimens and no patient showed any neurological sequelae.

ARTERIAL PRESSURE (fig. 1)

MAP decreased significantly in all three groups during surgery ($P < 0.01$) and after 40 min of surgery was 53, 55 and 55 mm Hg in the isoflurane, trimetaphan and nitroprusside groups, respectively. In the postoperative period, rebound hypertension did not occur and MAP was not significantly different from control values. There were no significant differences between the three groups.

METABOLITES

Blood glucose (fig. 2)

Significant increases in blood glucose concentration were found in the isoflurane group ($P < 0.05$, 20 and 40 min of surgery) and nitroprusside group ($P < 0.05$, 40 min of surgery, $P < 0.01$, 30 min recovery). In contrast, the small increase in blood glucose in the trimetaphan group (5.3–6.1 mmol $litre^{-1}$) failed to reach statistical significance. There were, however, no significant differences between the groups.

Blood lactate and pyruvate (table 2)

There was a small increase in lactate concentrations in all three groups with the onset of hypotension and surgery, but this change was not significant. In the postoperative period lactate concentrations declined and this change was significant in the isoflurane and trimetaphan groups ($P < 0.01$). There were no significant differences in lactate values between the three groups.

There were no significant changes in blood pyruvate concentrations within and between groups during the study.

Plasma NEFA (table 2)

Circulating NEFA concentrations decreased significantly in all three groups ($P < 0.01$, 20 min of surgery in the isoflurane and trimetaphan groups, and $P < 0.01$, 30 min recovery in the nitroprusside group). There were no significant differences between the three groups.

Table 1 Patient details (mean (SEM or range) or number)

	Group I (isoflurane) ($n = 9$)	Group II (trimetaphan) ($n = 9$)	Group III (SNP) ($n = 10$)
Age (yr)	43 (24–59)	39 (29–58)	32 (21–47)
Sex (M:F)	4:5	2:7	6:4
Body mass index (kg m^{-2})	22.6 (1.7)	23.7 (1.2)	24.0 (0.8)
Time of surgery (am:pm)	6:3	5:4	7:3
Duration of starvation (h)	11 (1.0)	9 (0.9)	10 (0.8)
Propranolol dose (mg)	2.9 (0.21)	3.0 (0.23)	3.4 (0.09)
Dose of hypotensive agent (mg min^{-1})		0.3 (0.07)	0.18 (0.06)
Duration of hypotension (min)	105 (19)	85 (10)	87 (6)
Type of surgery (n)	Myringoplasty (5) Stapedectomy (1) Mastoidectomy (2) Tympanotomy (1)	Myringoplasty (7) Stapedectomy (1) Tympanoplasty (1)	Myringoplasty (4) Stapedectomy (2) Mastoidectomy (1) Tympanotomy (1) Tympanoplasty (1) Ossiculoplasty (1)

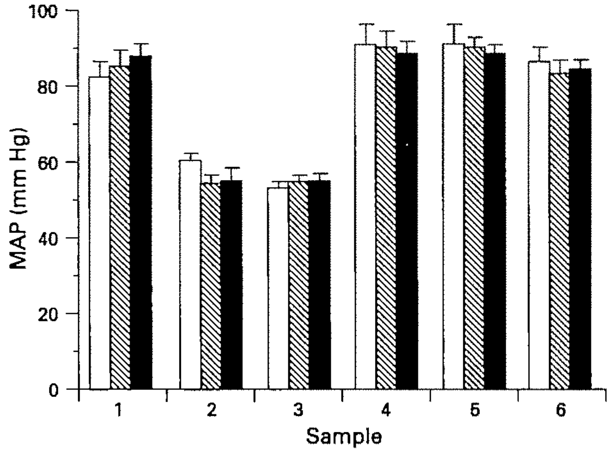


Figure 1 Mean (SEM) mean arterial pressure (MAP) in the isoflurane (□), trimetaphan (▨) and sodium nitroprusside (■) groups. Sample 1 = control, 2 = 20 min of surgery, 3 = 40 min of surgery, 4, 5 and 6 = 30, 60 and 120 min, respectively, after restoration of normal MAP.

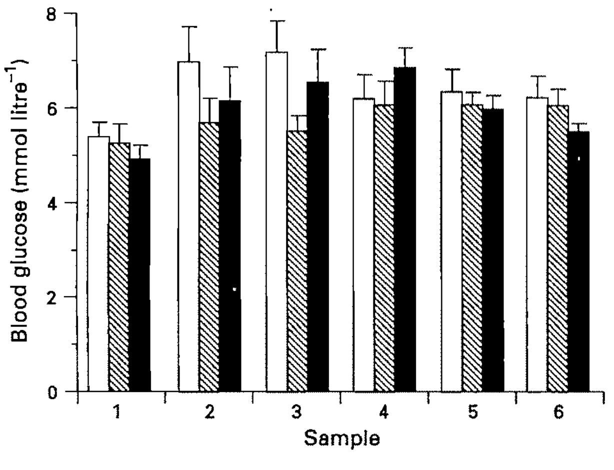


Figure 2 Mean (SEM) blood concentrations in the isoflurane (□), trimetaphan (▨) and sodium nitroprusside (■) groups. Sample 1 = control, 2 = 20 min of surgery, 3 = 40 min of surgery, 4, 5 and 6 = 30, 60 and 120 min, respectively, after restoration of normal MAP.

Plasma uric acid (table 2)

Uric acid values increased significantly after 40 min of surgery and 60 min recovery in the isoflurane group ($P < 0.05$), and after 60 min recovery in the trimetaphan group ($P < 0.05$). There were no significant differences between the three groups.

HORMONES

Serum cortisol (fig. 3)

Serum cortisol concentrations increased during surgery in all groups, but this change was significant only in the nitroprusside group ($P < 0.01$, 40 min of surgery). However, significant increases occurred in all three groups after 30 and 60 min recovery ($P < 0.05$ isoflurane and trimetaphan, $P < 0.01$ nitroprusside). There were no significant differences between the groups.

Serum GH (table 2)

GH concentration increased significantly in all groups after only 20 min of surgery ($P < 0.01$) and declined slowly in the postoperative period. There were no significant differences between the groups.

Serum insulin (table 2)

Insulin values decreased during surgery, but this change was significant only in the trimetaphan ($P < 0.05$, 20 and 40 min of surgery) and nitroprusside ($P < 0.01$, 20 min and $P < 0.05$, 40 min of surgery) groups. There were no significant differences in insulin values between the three groups.

Packed cell volume

PCV declined significantly in all three groups ($P < 0.05$ isoflurane, $P < 0.01$ trimetaphan, nitroprusside), but there were no significant differences between groups.

Discussion

All three groups of patients showed a typical metabolic and hormonal response to surgery with an increase in circulating glucose, cortisol and GH concentrations. The size and duration of the response were similar to that described in other forms of

Table 2 Mean (SEM) blood lactate and pyruvate concentrations (mmol litre^{-1}), plasma NEFA and uric acid concentrations (mmol litre^{-1}), and serum insulin values (mu litre^{-1}). Median (range) GH values (mu litre^{-1}). Significant differences from control: $*P < 0.05$, $**P < 0.01$

	Sample No.											
	1 Control		2 20 min surgery		3 40 min surgery		4 30 min recovery		5 60 min recovery		6 120 min recovery	
Lactate												
Isoflurane	1.12	(0.18)	1.34	(0.13)	1.14	(0.13)	0.84	(0.06)	0.62**	(0.08)	0.50**	(0.10)
Trimetaphan	0.91	(0.10)	0.94	(0.09)	0.84	(0.08)	0.61**	(0.10)	0.50**	(0.08)	0.42**	(0.08)
Nitroprusside	0.74	(0.11)	0.93	(0.14)	0.90	(0.10)	0.92	(0.17)	0.58	(0.06)	0.49	(0.06)
Pyruvate												
Isoflurane	0.110	(0.019)	0.128	(0.022)	0.156	(0.031)	0.098	(0.014)	0.095	(0.017)	0.074	(0.017)
Trimetaphan	0.123	(0.019)	0.110	(0.017)	0.130	(0.027)	0.091	(0.024)	0.112	(0.025)	0.092	(0.023)
Nitroprusside	0.134	(0.018)	0.148	(0.023)	0.089	(0.014)	0.104	(0.020)	0.110	(0.023)	0.083	(0.014)
NEFA												
Isoflurane	1.00	(0.123)	0.52**	(0.067)	0.59**	(0.055)	0.50**	(0.076)	0.53**	(0.87)	0.56**	(0.650)
Trimetaphan	1.04	(0.095)	0.76**	(0.059)	0.84	(0.087)	0.65**	(0.081)	0.72**	(0.93)	0.64**	(0.610)
Nitroprusside	0.90	(0.082)	0.73	(0.101)	0.84	(0.083)	0.60**	(0.041)	0.61**	(0.047)	0.62**	(0.330)
Uric acid												
Isoflurane	0.248	(0.055)	0.266	(0.53)	0.289*	(0.061)	0.259	(0.055)	0.285*	(0.065)	0.271	(0.055)
Trimetaphan	0.215	(0.010)	0.208	(0.007)	0.233	(0.022)	0.253	(0.032)	0.265*	(0.028)	0.231	(0.016)
Nitroprusside	0.289	(0.036)	0.285	(0.037)	0.286	(0.039)	0.287	(0.034)	0.306	(0.040)	0.296	(0.035)
Insulin												
Isoflurane	18.8	(3.6)	14.7	(2.4)	15.3	(2.4)	19.7	(2.9)	16.5	(3.2)	16.9	(3.4)
Trimetaphan	18.8	(5.6)	11.5*	(4.0)	11.9*	(3.7)	14.5	(3.1)	13.2	(3.1)	15.4	(3.6)
Nitroprusside	19.3	(3.8)	12.5**	(2.9)	13.5**	(2.7)	15.5	(3.2)	16.3	(3.5)	15.3	(2.6)
GH												
Isoflurane	1.0 (0.5–3.3)		11.6** (0.5–28)		11.8** (0.5–33)		3.9* (0.5–42)		9.2** (1.0–47)		14.9** (1.0–59.6)	
Trimetaphan	1.0 (0.5–4.4)		7.3** (1.0–14.3)		8.2* (1.0–25)		5.8** (1.0–26)		4.3 (1.0–73.8)		4.6 (0.5–68.9)	
Nitroprusside	1.0 (0.5–5.5)		9.9** (3.1–51)		12.9** (1.6–61)		6.5** (1.0–15.1)		6.4* (1.0–48.4)		3.9* (0.6–10.3)	

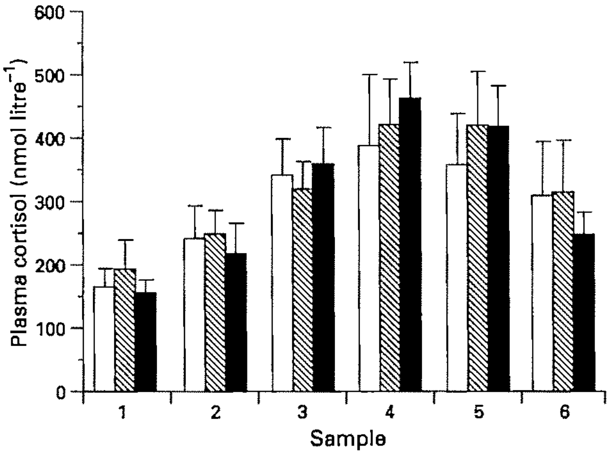


Figure 3 Mean (SEM) plasma cortisol concentrations in the isoflurane (□), trimetaphan (▧) and sodium nitroprusside (■) groups. Sample 1 = control, 2 = 20 min of surgery, 3 = 40 min of surgery, 4, 5 and 6 = 30, 60 and 120 min, respectively, after restoration of normal MAP.

"low-stress" surgery such as ophthalmic and surface surgery [9]. However, there were no significant differences between the three techniques of induced hypotension in their effects on the metabolic and hormonal changes. This finding was unexpected, as the use of nitroprusside during hypotensive anaesthesia has been shown to increase markedly circulating catecholamines during surgery compared with administration of trimetaphan [2]. It is possible that the use of propranolol i.v. before induction of anaesthesia may have attenuated any difference in sympathoadrenal response. Khambatta and colleagues [10] found that premedication with propranolol decreased the release of catecholamines resulting from nitroprusside-induced hypotension. Nevertheless, the trimetaphan group was the only group that failed to show a significant increase in blood glucose concentrations, suggesting a diminished sympathetic response. A similar effect on the glucose response to surgery was found when pentolinium was used to induce hypotension for hip surgery [11].

The abrupt decline in plasma NEFA values was an unusual observation in studies of the metabolic response to surgery. It has also been found after i.v. infusion of the potent antilipolytic hormone, insulin [12]. In the present study, it is likely that propranolol resulted in the decrease in NEFA concentrations. The triacylglycerol lipase enzyme in adipose tissue is particularly sensitive to β adrenoceptor stimulation through the adenyl cyclase–cyclic AMP pathway [13].

Circulating lactate concentrations represent the balance between the production and utilization of a metabolite with a high turnover rate of approximately 1.2 mol day^{-1}. Alterations in blood concentration may be difficult to interpret, but it has been suggested that the typical lactate response to surgery at normal arterial pressure reflects an increase in sympathoadrenal activity [12]. This hyperlactataemia is associated with increased muscle glycogenolysis and hence lactate production, and is ameliorated by anaesthetic techniques, such as extradural analgesia and high-dose opioid anaesthesia, that are known to reduce the catecholamine response to surgery [6, 14]. With a decrease in MAP to 55 mm Hg during surgery in the present study, we expected an increase in circulating lactate as a result of cellular hypoxia, decreased hepatic and renal perfusion, or both. However, there was no significant change during surgery and a significant *decrease* in the postoperative period, possibly as a consequence of β adrenoceptor block.

Increase in circulating uric acid has been suggested as an indicator of cellular hypoxia [15]. Loss of adenosine triphosphate and its degradation to purine metabolites leads to an increase in uric acid production during hypotensive events [16]. Although we observed the occasional significant increase in plasma uric acid, all values remained within the normal range (< 0.4 mmol litre^{-1}). Our results suggest that, on the basis of two biochemical indices of hypoxia, lactate and urate, oxygen delivery is adequate during normovolaemic hypotension in healthy patients. However, regional hypoperfusion cannot be excluded.

There was a rapid increase in GH secretion to values seen commonly in major abdominal surgery [8]. In contrast, mean cortisol concentrations remained less than 500 nmol litre^{-1}. It is possible that the concomitant use of propranolol modified pituitary hormone secretion. In humans, it is clear that GH secretion is stimulated by α_2 adrenoceptors and inhibited by β adrenoceptors, but the effects of adrenergic drugs on ACTH secretion are ambiguous [17].

In conclusion, the use of induced hypotension for middle ear surgery is associated with a metabolic and endocrine response which is modified in part by the concomitant use of a β adrenoceptor blocking drug. Our study did not allow us to differentiate between the specific effects of surgical stimulation, induced hypotension and propranolol. We speculate that normovolaemic induced hypotension in healthy patients after propranolol may not trigger catabolic hormone secretion in the absence of surgery.

Acknowledgements

We thank the Joint Research Committee and Special Trustees of the Royal National Throat, Nose and Ear Hospital for their generous financial support.

References

1. Hall GM. Endocrine and metabolic responses to surgery and anaesthesia. In: Nimmo WS, Rowbotham DJ, Smith G, eds. *Anaesthesia*, 2nd Edn. Oxford: Blackwell, 1994; 595–605.
2. Knight PR, Lane GA, Hensinger RN, Bolles RS, Bjoraker DG. Catecholamine and renin–angiotensin response during hypotensive anaesthesia induced by sodium nitroprusside or trimetaphan camsylate. *Anesthesiology* 1983; **59**: 248–253.
3. Bernard J-M, Pinaud M, Maquin-Mavier I, Remi J-P, Passuti N. Hypotensive anesthesia with isoflurane and enflurane during total hip replacement. A comparative study of catecholamine and renin responses. *Anesthesia and Analgesia* 1989; **69**: 467–472.
4. Toivonen J. Plasma renin, catecholamines, vasopressin and aldosterone during hypotension induced by labetalol with isoflurane. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 496–501.

5. Engquist A, Fog-Møller F, Christiansen C, Thode J, Vester-Andersen T, Nistrup Madsen S. Influence of epidural analgesia on the catecholamine and cyclic AMP responses to surgery. *Acta Anaesthesiologica Scandinavica* 1980; **24**: 17–21.
6. Hall GM, Young C, Holdcroft A, Alaghband-Zadeh J. Substrate mobilisation during surgery. A comparison between halothane and fentanyl anaesthesia. *Anaesthesia* 1978; **33**: 924–930.
7. Fossati P, Prencipe L, Berti G. Use of 3,5-dichloro-2-hydroxybenzenesulfonic acid/4-aminophenazone chromogenic system in direct enzymic assay of uric acid in serum and urine. *Clinical Chemistry* 1980; **26**: 227–231.
8. Moore CM, Desborough JP, Powell H, Burrin JM, Hall GM. Effects of extradural anaesthesia on interleukin-6 and acute phase response to surgery. *British Journal of Anaesthesia* 1994; **72**: 272–279.
9. Chernow B, Alexander B, Smallridge RC, Thompson WR, Cook D, Beardsley D, Fink MP, Lake R, Fletcher R. Hormonal responses to graded surgical stress. *Archives of Internal Medicine* 1987; **147**: 1273–1278.
10. Khambatta HJ, Stone JG, Matteo RS, Khan E. Propranolol premedication blunts stress response to nitroprusside hypotension. *Anesthesia and Analgesia* 1984; **63**: 125–128.
11. Fahmy NR, Battit GE. Effects of pentolinium on blood sugar and serum potassium concentrations during anaesthesia and surgery. *British Journal of Anaesthesia* 1975; **47**: 1309–1314.
12. Hall GM, Walsh ES, Paterson JL, Mashiter K. Low-dose insulin infusion and substrate mobilisation during surgery. *British Journal of Anaesthesia* 1983; **55**: 939–945.
13. Newsholme EA, Leech AR. *Biochemistry for the Medical Sciences* Chichester: John Wiley and Sons, 1983.
14. Kehlet H. The modifying effect of general and regional anaesthesia on the endocrine–metabolic respones to surgery. *Regional Anaesthesia* 1982; 7: 538–548.
15. Fox HI, Palella TD, Kelley WN. Hyperuricemia. A marker for cell energy crisis. *New England Journal of Medicine* 1987; **317**: 111–112.
16. Woolliscroft JO, Fox HI. Increased body fluid purine levels during hypotensive events. *American Journal of Medicine* 1986; **81**: 472–478.
17. Al-Damluji S. Adrenergic control of the secretion of anterior pituitary hormones. *Clinical Endocrinology and Metabolism* 1993; 7: 355–392.

British Journal of Anaesthesia 1996; **76**: 358–361

Influence of dose and timing of administration of morphine on postoperative pain and analgesic requirements

M. D. MANSFIELD, K. S. JAMES AND J. KINSELLA

Summary

In a randomized, double-blind study, we have investigated the effect of dose and timing of administration of morphine on postoperative pain and analgesic requirements in 60 patients undergoing hysterectomy, with or without salpingo-oophorectomy. Patients were allocated randomly to one of three groups: during standardized general anaesthesia, group post received morphine 0.15 mg kg^{-1} i.v. at peritoneal closure after hysterectomy; group pre-low received morphine 0.15 mg kg^{-1} on induction of anaesthesia; and group pre-high received morphine 0.3 mg kg^{-1} on induction of anaesthesia. Median postoperative morphine consumption (first 24 h) from a PCA system was 68 mg (group post), 56 mg (group pre-low) and 43 mg (group pre-high), and total perioperative morphine consumption (induction of anaesthesia to end of 24 h after surgery) was 77 mg (group post), 65 mg (group pre-low) and 63 mg (group pre-high). Pain scores (at rest and on movement) were similar in the three groups. A large dose of morphine 0.3 mg kg^{-1} i.v. on induction of anaesthesia significantly reduced postoperative PCA morphine requirements compared with the smaller dose (0.15 mg kg^{-1}) administered at induction or peritoneal closure, in patients undergoing hysterectomy, with or without salpingo-oophorectomy. (*Br. J. Anaesth.* 1996; **76**: 358–361)

Key words

Pain, postoperative. Analgesia, pre-emptive. Analgesics opioid, morphine. Surgery, gynaecological.

Management of pain after surgery is often inadequate but optimal pain relief is important as it may reduce postoperative complications and speed recovery and discharge of patients from hospital [1]. Increasing attention is now being focused on strategies to reduce, or even abolish, postoperative pain.

The objective of pre-emptive analgesia is to prevent reflex central neuronal hyperexcitability which occurs in the spinal cord in response to the afferent barrage from peripheral nociceptors after a noxious stimulus [2, 3]. When established, this central sensitization is difficult to suppress, and may make effective pain relief difficult or impossible to achieve [3]. Laboratory work in animals has shown that it is possible to reduce, or even block completely, spinal cord hyperactivity in response to a painful stimulus, using either local anaesthetics [4, 5] or opioids [6].

Various pre-emptive strategies have been used with opioid analgesics [7–11], local anaesthetics [7, 12–14] and *N*-methyl-D-aspartate receptor antagonists [15]. While some studies have supported a pre-emptive analgesic effect, others have been unable to demonstrate an effect clinically. We have attempted to confirm the findings of a study on patients undergoing hysterectomy [9] which showed a pre-emptive effect with morphine 10 mg administered on induction of anaesthesia, compared with giving the same dose at peritoneal closure. In addition, we investigated the difference between two doses of morphine, administered pre-emptively, on postoperative pain and analgesic requirements. An abstract of this work has been published previously [16].

Patients and methods

After obtaining local hospital Ethics Committee approval, we studied in a double-blind, randomized study, female patients, ASA I or II, aged 18–70 yr, weighing 45–100 kg, undergoing total abdominal hysterectomy, with or without salpingo-oophorectomy. The use of a patient-controlled analgesia system (PCAS) (Graseby Medical, Watford, UK), visual analogue scales and verbal rating scores was explained on the evening before surgery. All patients provided written informed consent, and recruitment continued until 60 evaluable patients had been included. We included only patients whose surgery was performed through a Pfannenstiel incision. Exclusion criteria were: patient request; any significant organ dysfunction; history of chronic pain; regular medication with any opioid or non-steroidal anti-inflammatory preparation; drug or alcohol abuse; or psychiatric disorder.

Before starting the study our hospital pharmacy prepared 75 pairs of ampoules, each ampoule

---

MARTIN D. MANSFIELD*, MB, CHB, FRCA, KENNETH S. JAMES, MB, CHB, FRCA, JOHN KINSELLA, MB, BS, FRCA, Directorate of Anaesthesia, Glasgow Royal Infirmary University NHS Trust, 84 Castle Street, Glasgow G4 0SF and University Department of Anaesthesia, Glasgow Royal Infirmary NHS Trust, 8–16 Alexandra Parade, Glasgow G31 2ER. Accepted for publication: October 10, 1995.

*Address for correspondence: Directorate of Anaesthesia, Glasgow Royal Infirmary University NHS Trust, 84 Castle Street, Glasgow G4 0SF.

containing 10 ml of colourless solution. Each pair of ampoules was boxed and numbered consecutively, 1 to 75, and comprised one ampoule labelled "induction" and one labelled "closure". Pairs of ampoules contained one of three possible combinations: Group post: placebo in the induction ampoule, morphine 1.5 mg ml^{-1} in the closure ampoule; Group pre-low: morphine 1.5 mg ml^{-1} in the induction ampoule, placebo in the closure ampoule; and Group pre-high: morphine 3 mg ml^{-1} in the induction ampoule, placebo in the closure ampoule. All investigators were blinded as to the contents of the pairs of ampoules; the only codes to randomization were held in the pharmacy. Each patient was allocated randomly by being allocated the next pair of consecutively numbered ampoules.

All patients received premedication with temazepam 20 mg orally, approximately 90 min before operation. Routine monitoring comprised electrocardiography, non-invasive arterial pressure and pulse oximetry. Patients received a standardized general anaesthetic with induction of anaesthesia with propofol 2 ml kg^{-1}. Immediately after induction, patients received 0.1 mg kg^{-1} i.v. from the ampoule labelled "induction". Neuromuscular block was achieved with vecuronium 0.1 mg kg^{-1} and anaesthesia maintained with isoflurane and 66 % nitrous oxide in oxygen. After tracheal intubation, patients were transferred to the operating theatre and surgery commenced. After completion of the hysterectomy, as the surgeon started to close the peritoneum, all patients received 0.1 ml kg^{-1} i.v. from the ampoule labelled "closure". Surgery was completed and patients transferred to the recovery area.

During operation, patients received one of three analgesic regimens: group post: placebo on induction, morphine 0.15 mg kg^{-1} on closure; group pre-low: morphine 0.15 mg kg^{-1} on induction, placebo on closure; and group pre-high: morphine 0.3 mg kg^{-1} on induction, placebo on closure.

After operation patients were made comfortable in the recovery area with incremental i.v. morphine boluses, administered by one of the investigators, and then returned to the ward with a PCAS containing morphine (1-mg bolus with a 5-min lockout time and no background infusion). Twenty-four hours after surgery the PCAS was removed, as is routine practice in our institution, and patients then received diclofenac suppositories, 100 mg every 12 h. Co-proxamol was available for breakthrough pain in the second 24 h if required.

Pain was assessed at 1, 2, 4, 24 and 48 h after operation using visual analogue scales (VAS) for pain at rest and on movement (0 mm = no pain, 100 mm = worst pain ever had), and an eight-point verbal rating score for pain at rest (no pain = 0, just noticeable = 1, mild = 2, weak = 3, moderate = 4, strong = 5, severe = 6, excruciating = 7, same random word display shown to each patient). For pain on movement patients were asked to take a deep breath followed by a cough.

I.v. morphine administered by the investigator in the recovery room and total 24-h PCAS morphine consumption were recorded, together with analgesic consumption in the second 24 h after operation. Side effects, including nausea and vomiting, and requirements for antiemetic drugs were noted.

The Kruskal–Wallis test followed by the Mann–Whitney *U* test were used to compare total 24-h postoperative morphine consumption in the three groups. The area under the curve over time was calculated for visual analogue scores for pain intensity at rest and on coughing in individual patients. These summary data were then subjected to Kruskal–Wallis and Mann–Whitney *U* tests as appropriate [17]. The incidence of side effects was compared by chi-square test. Statistical analyses were performed in Minitab release 9.2. In all cases $P < 0.05$ was considered to indicate significance.

Results

Sixty-six patients were recruited in total and six were withdrawn because of: midline incision (two patients in group post), possible allergic reaction to morphine (one patient in group pre-high), severe anxiety altering the anaesthetic technique (one patient in group post) and further surgery within first 6 h after operation (two patients in group pre-high). The possible morphine allergy was evidenced by marked erythema of the face and neck with mild facial oedema, and was noted 4 h after operation. Patient-controlled analgesia was discontinued immediately and substituted with pethidine by intermittent i.m. bolus injection. The patient was not distressed, and the signs dissipated gradually over approximately 4 h.

Patient characteristics and type and duration of operation performed were similar in the three groups (table 1). The apparent difference in total postoperative morphine consumption (table 1) between the post and pre-low groups was not statistically significant. Patients in group pre-high used significantly less morphine in the first 24 h after surgery compared with patients in group post ($P = 0.0002$) and group pre-low ($P = 0.0016$). Total perioperative morphine consumption (i.e. allowing for additional i.v. morphine given during operation in group pre-high) was still significantly less in group pre-high compared with group post ($P = 0.018$) but not with group pre-low ($P = 0.27$). There were no differences between the groups in analgesic requirements in the second 24 h after operation.

Table 1 Patient characteristics, operation type and morphine use (median (interquartile range) or absolute values)

	Group		
	Post ($n = 18$)	Pre-low ($n = 22$)	Pre-high ($n = 20$)
Age (yr)	45 (41–48)	43 (39–49)	42 (36–46)
Weight (kg)	61 (55–65)	61 (55–68)	64 (60–70)
Duration of op. (min)	66 (46–83)	60 (49–67)	55 (51–78)
Hysterectomy	4	5	6
Hysterectomy + BSO	14	17	14
24-hour postoperative morphine use (mg)	68 (56–92)	56 (50–75)	43 (30–53)
Total perioperative morphine use (mg)	77 (65–102)	65 (60–84)	63 (51–73)

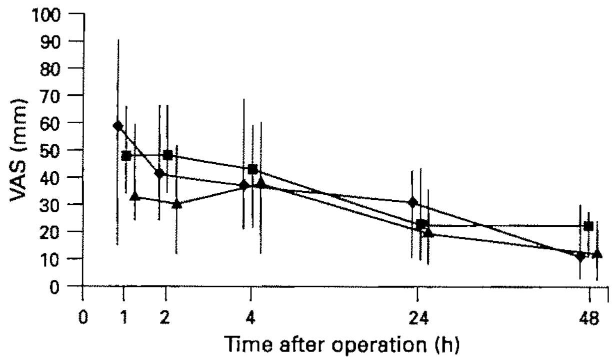


Figure 1 Visual analogue scores (VAS) for pain at rest (median, interquartile range) for group post (◆), group pre-low (■) and group pre-high (▲).

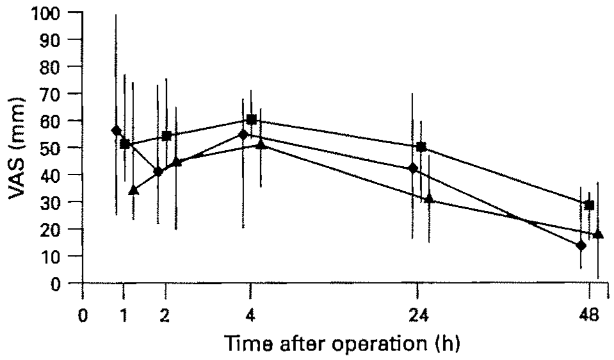


Figure 2 Visual analogue scores (VAS) for pain on coughing (median, interquartile range) for group post (◆), group pre-low (■) and group pre-high (▲).

Visual analogue scores for pain at rest and on movement are shown in figures 1 and 2. There were no significant differences between VAS at rest or on coughing, or verbal rating scores for pain at rest, in the three groups.

The incidences of nausea and vomiting were unacceptably high with 67% (group post), 59% (group pre-low) and 85% (group pre-high) of patients experiencing some degree of nausea or vomiting in the first 24 h after operation. Antiemetic therapy was required at least once by 44% (group post), 41% (group pre-low) and 60% (group pre-high) of patients. There were no significant differences in the incidence of nausea or emesis in the three groups.

Discussion

Only one study to date [9] has shown a clear pre-emptive analgesic effect using a simple opioid regimen. In that study it was found that morphine 10 mg i.v. significantly reduced postoperative PCA morphine consumption when administered on induction of anaesthesia compared with the same dose at the time of peritoneal closure. We have been unable to confirm this finding. In another study the same group [10] reached the conclusion that there was no clinical benefit in increasing the dose of pre-emptive analgesia. They also found that more sedation and an increased incidence of nausea and vomiting were sequelae of a larger dose of morphine.

Pre-emptive analgesia depends on reduction or prevention of central neuronal hyperexcitability (wind-up) which occurs in the spinal cord in response to peripheral nociceptive inputs. In the case of morphine analgesia, this is mediated by μ receptor stimulation. It has been shown that spinal cord wind-up begins almost immediately after a nociceptive stimulus [6], and thus any pre-emptive analgesic administered must be stimulating μ receptors at the commencement of such a stimulus. It is possible that a large dose of i.v. morphine may flood spinal opioid receptors more rapidly and to a greater extent than a smaller dose, and that this might result in a greater pre-emptive analgesic effect.

This possible explanation concurs with the findings in our study where group pre-high used 37% less morphine than group post, and 23% less than group pre-low in the first 24 h after operation. Obviously, group pre-high received twice as much intraoperative morphine as the two other groups but, even allowing for this, they still used 18% less morphine than group post in the perioperative period and this was statistically significant.

There was an unacceptably high incidence of nausea, vomiting, or both, in our study. Prochlorperazine was available to all patients after operation but we did not administer any intraoperative antiemetic. It should be stressed that even mild nausea was recorded, but 60% of patients in group pre-high required prochlorperazine at least once.

If the main purpose of intraoperative analgesia is to make patients more comfortable in the postoperative period (or permit an equal degree of comfort requiring less analgesic medication) then we conclude that a large dose of morphine administered on induction of anaesthesia significantly reduces postoperative morphine requirements from a PCA machine compared with a smaller dose given on induction of anaesthesia or at the time of abdominal closure.

References

1. Commission on the provision of surgical services. *Report of the Working Party on Pain After Surgery*. London: The Royal College of Surgeons of England, The College of Anaesthetists, September 1990.
2. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature (London)* 1983; **306**: 686–688.
3. Woolf CJ, Wall PD. Morphine-sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. *Neuroscience Letters* 1986; **64**: 221–225.
4. Coderre TJ, Melzack R. Cutaneous hyperalgesia: contributions of the peripheral and central nervous systems to the increase in pain sensitivity after injury. *Brain Research* 1987; **404**: 95–106.
5. Coderre TJ, Vaccarino AL, Melzack R. Central nervous system plasticity in the tonic pain response to subcutaneous formalin injection. *Brain Research* 1990; **535**: 155–158.
6. Dickenson AH, Sullivan AF. Subcutaneous formalin-induced activity of dorsal horn neurones in the rat: differential response to an intrathecal opiate administered pre or post formalin. *Pain* 1987; **30**: 349–360.
7. McQuay HJ, Carroll D, Moore RA. Postoperative orthopaedic pain—the effect of opiate premedication and local anaesthetic blocks. *Pain* 1988; **33**: 291–295.

8. Kiss IE, Kilian M. Does opiate premedication influence postoperative analgesia? A prospective study. *Pain* 1992; **48**: 157–158.
9. Richmond CE, Bromley LM, Woolf CJ. Preoperative morphine pre-empts postoperative pain. *Lancet* 1993; **342**: 73–75.
10. Collis R, Brandner B, Bromley LM, Woolf CJ. Is there any clinical advantage of increasing the pre-emptive dose of morphine or combining pre-incisional with postoperative morphine administration? *British Journal of Anaesthesia* 1995; **74**: 396–399.
11. Mansfield M, Meikle R, Miller C. A trial of pre-emptive analgesia. Influence of timing of peroperative alfentanil on postoperative pain and analgesic requirements. *Anaesthesia* 1994; **49**: 1091–1093.
12. Pryle BJ, Vanner RG, Enriquez N, Reynolds F. Can pre-emptive lumbar epidural blockade reduce postoperative pain following lower abdominal surgery? *Anaesthesia* 1993; **48**: 120–123.
13. Jebeles JA, Reilly JS, Gutierrez JF, Bradley EL, Kissin I. The effect of pre-incisional infiltration of tonsils with bupivacaine on the pain following tonsillectomy under general anaesthesia. *Pain* 1991; **47**: 305–308.
14. Ejlerson E, Andersen HB, Eliasen K, Mogensen T. A comparison between preincisional and postincisional lidocaine infiltration and postoperative pain. *Anesthesia and Analgesia* 1992; **74**: 495–498.
15. Tverskoy M, Oz Y, Isakson A, Finger J, Bradley EL jr, Kissin I. Preemptive effect of fentanyl and ketamine on postoperative pain and wound hyperalgesia. *Anesthesia and Analgesia* 1994; **78**: 205–209.
16. Mansfield MD, James KS, Kinsella J. Influence of dosage and timing of peroperative morphine on postoperative pain and analgesic requirements. *British Journal of Anaesthesia* 1995; 74 (Suppl. 1): 136.
17. Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *British Medical Journal* 1990; **300**: 230–235.

British Journal of Anaesthesia 1996; **76**: 362–364

Recovery after desflurane anaesthesia in the infant: comparison with isoflurane

A. R. WOLF, R. A. LAWSON, C. M. DRYDEN AND F. W. DAVIES

Summary

We have studied 20 infants, aged 2.5–8 weeks, undergoing general anaesthesia for pyloromyotomy with either desflurane or isoflurane. Patients were anaesthetized with equivalent 1 MAC values for age and agent. A blinded observer recorded times to breathing, swallowing, movement, extubation and side effects after discontinuation of the agent. Recovery times in the desflurane group were significantly shorter than in the isoflurane group. The times to swallowing, movement and extubation in the desflurane group were 3.89 (SD 2.4) min, 5.33 (4.95) min, 7.5 (4.53) min, respectively, and 8.82 (2.40) min, 10.73 (3.93) min, 13.45 (4.20) in the isoflurane group. In addition, postoperative apnoea was documented in the isoflurane group but not in those infants receiving desflurane. There was no laryngospasm after extubation in either group. We conclude that desflurane possesses useful characteristics for recovery conditions in the infant and may be particularly useful in the ex-premature infant prone to apnoea and ventilatory depression. (*Br. J. Anaesth.* 1996; **76**: 362–364)

Key words

Anaesthesia, paediatric. Anaesthetics volatile, isoflurane. Anaesthetics volatile, desflurane.

Neonates are susceptible to ventilatory depression after general anaesthesia [1] and this results partly from the residual effects of the volatile agent [2]. Isoflurane is often used in preference to halothane in the neonate because of its more rapid recovery characteristics. However, desflurane, a relatively new short-acting volatile agent, may confer further advantages with respect to quality of recovery. Desflurane has a blood:gas solubility of 0.42 [3] which should be associated with a more rapid recovery than isoflurane which has a blood:gas solubility of 1.4 [4]. Its use in paediatric anaesthesia has been limited by concerns about laryngospasm and breath-holding during inhalation induction. However, these effects are less relevant in neonates because the trachea is usually intubated on induction and the lungs ventilated during surgery. Taylor and Lerman demonstrated that these complications do not occur at extubation [5].

We therefore hypothesized that desflurane anaesthesia in infants would be associated with faster recovery than isoflurane even after a relatively short period of general anaesthesia and that there would be fewer postoperative ventilatory complications.

Patients and methods

After obtaining Ethics Committee approval and informed parental consent, we studied 20 patients undergoing pyloromyotomy. Patients were allocated randomly, using random number tables, to receive either isoflurane (even numbers) or desflurane (odd numbers) anaesthesia. No premedication was given and anaesthesia was induced with thiopentone 1.5 mg kg^{-1} and suxamethonium 1.5 mg kg^{-1} using a modified rapid sequence induction. Immediately after tracheal intubation, atracurium 0.5 mg kg^{-1} was administered and the lungs ventilated to normocapnia with 1 MAC of desflurane (9.16% neonates, 9.42% infants) [6] or isoflurane (1.6% neonates, 1.87% infants) [7] in 100% oxygen. Heart rate, arterial pressure and rectal temperature were recorded at 5-min intervals throughout the procedure. A normal value of 80 mm Hg for systolic arterial pressure in the awake neonate was used as baseline given the variability [8] and difficulty in recording accurate non-invasive readings in the unpremedicated awake infant. End-tidal concentrations of carbon dioxide and volatile agent were monitored (Datex Capnomac Ultima). End-tidal volatile agent was maintained at 1 MAC until surgery was finished, local anaesthetic had been infiltrated and residual neuromuscular block antagonized with neostigmine 40 μg kg^{-1} and atropine 20 μg kg^{-1}. The infant was then left undisturbed and normocapnia maintained with 100% oxygen. The onset of swallowing, breathing, movement and time to extubation were recorded by an observer blinded to the agent used. Perioperative and immediate postoperative ventilatory complications were documented. Breath-holding was defined as coughing and straining on the tracheal tube, and significant apnoea was regarded as a period of 15 s or more occurring after extubation.

A. R. WOLF*, MBCHIR, FRCA, R. A. LAWSON, MB, CHB, FRCA, C. M. DRYDEN, MB, CHB, FRCA, F. W. DAVIES, MB, CHB, FFARSCI, Department of Anaesthesia, Royal Hospital for Sick Children, Yorkhill NHS Trust, Glasgow G3 8SJ. Accepted for publication: October 20, 1995.

*Present address for correspondence: Department of Anaesthesia, Royal Hospital for Sick Children, St Michael's Hill, Bristol BS2 8BJ.

Because of the relatively small sample size, numerical data of times recorded to breathing, swallowing, movement and extubation were analysed using the Mann–Whitney *U* test. Nominal data were analysed using the chi-square test with Yates' correction. $P < 0.05$ was considered significant.

Results

Both groups were comparable in age, weight and duration of surgery (table 1).

Figure 1 shows the times taken from discontinuation of the agent to breathing, swallowing, movement and extubation. The times taken to commence swallowing, movement and extubation were significantly shorter in the desflurane group ($P < 0.01$ for swallowing, $P < 0.05$ for movement and extubation).

Changes in heart rate and systolic arterial pressure are shown in figure 2. There was no statistical difference in heart rate or systolic arterial pressure between the two groups. Complications were recorded as a decrease in systolic pressure and breath-holding or apnoeic episodes. A decrease in systolic arterial pressure of more than 30 % from a normal neonatal awake value was regarded as clinically significant. Table 2 shows the number of patients in each group in which these complications occurred.

Discussion

We have observed that desflurane anaesthesia in the infant resulted in approximately twice the speed of recovery, in terms of breathing, swallowing, movement and extubation, compared with an equivalent MAC value of isoflurane. We have confirmed the finding [6] that 1 MAC of desflurane resulted in a decrease in systolic arterial pressure and that in 44 % of patients this was clinically significant (table 2). We have also shown that a similar decrease in systolic pressure occurred with isoflurane. The difference in systolic arterial pressure during surgery between the two groups was not significant in our study. However, given the small numbers in the groups and the large variability around the mean value, the power of the test was only 0.4. In order to reject the null hypothesis (that there was no difference in systolic arterial pressure between the two groups) a total of 250 patients would be required, assuming that the size of the difference between the two treatment groups remained the same [9]. The increased number of apnoeas noted in the isoflurane group may reflect slower recovery. The prolonged apnoeic episodes (> 15 s) noted were distinct from breath-holding which we had predefined. Taylor

Table 1 Patient characteristics (mean (SD or range))

	Desflurane group ($n = 9$)	Isoflurane group ($n = 11$)
Age (weeks)	3.87 (2–7)	4.91 (2–6)
Weight (kg)	3.64 (0.47)	3.53 (0.75)
Duration of surgery (min)	34.56 (6.50)	33.64 (5.18)

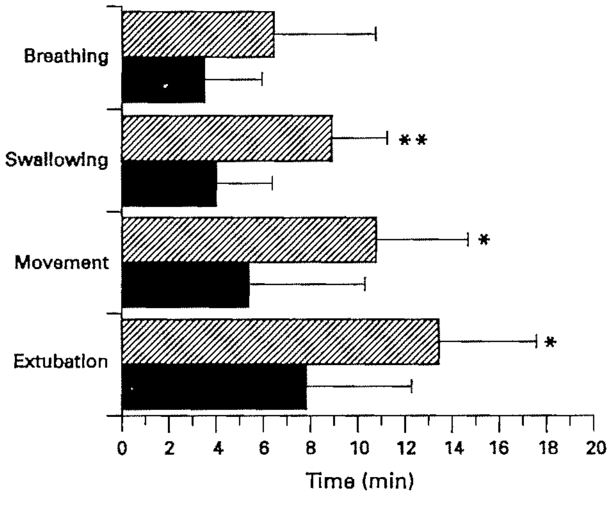


Figure 1 Recovery times (mean (SD) minutes) after discontinuation of the volatile agents isoflurane (▨) ($n = 11$) and desflurane (■) ($n = 9$). $*P < 0.05$, $**P < 0.01$.

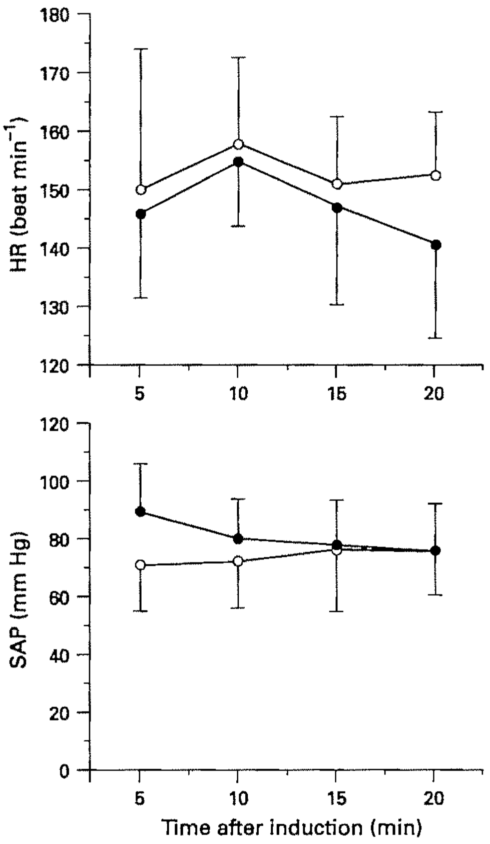


Figure 2 Mean (SD) measurements of heart rate (HR) and systolic arterial pressure (SAP) in the isoflurane (●) ($n = 11$) and desflurane (○) ($n = 9$) groups.

Table 2 Number of patients in each group with a decrease in systolic arterial pressure (SAP) (percentage decrease from normal value of 80 mm Hg) and number with ventilatory complications

	Isoflurane ($n = 11$)	Desflurane ($n = 9$)
Decrease in SAP ⩾ 10 %	9	7
Decrease in SAP ⩾ 30 %	3	4
Breath-holding	4	2
Apnoea	3	0

and Lerman have suggested that because of the speed of recovery after desflurane anaesthesia, airway complications at extubation are unlikely [5], and we are not aware of any cases documented in the paediatric literature.

The anaesthetic technique chosen did not attempt to reflect routine clinical practice for general anaesthesia for pyloromyotomy. It was used as a means of comparing the effects of isoflurane and disflurane at equivalent MAC values for a standard period of time in neonates undergoing a short surgical procedure. The technique was a model to allow us to determine the differences in recovery characteristics of these two agents. The slightly lesser dose of thiopentone than that recommended by Hatch and Sumner [10] was chosen to minimize the ventilatory depressant effects of any residual i.v. agent at the end of the procedure. In order to ensure standardization of the anaesthetic, an end-tidal concentration of 1 MAC of agent was maintained until completion of the operation. Thus there was no tailoring of MAC levels as might occur in practice and no external stimulation allowed in order to facilitate awakening. Although not studied formally, it was our clinical impression that patients in the isoflurane group were sleepier and slower to recover than those in the desflurane group. Longer term data on respiration and sedation in the postoperative period would be advantageous.

In many respects, desflurane appears to be an impractical agent. It is expensive, requires a special vaporizer, and in paediatric practice has been associated with significant ventilatory complications on inhalation [5, 6]. However, it has the desirable characteristics of rapid emergence from anaesthesia because of its low blood:gas and tissue:gas solubilities. While these properties may be of little benefit in routine paediatric anaesthesia for healthy children undergoing short procedures, they may become increasingly relevant in the ex-premature infant. These patients are at increased risk from postoperative ventilatory complications such as apnoeic spells, with an incidence correlating inversely with gestational age and weight [11, 12]. Inhalation and i.v. anaesthetic agents exacerbate this problem by depressing immature ventilatory control mechanisms. Central nervous system depressant effects may be reduced further if desflurane is used at a lower concentration than 1 MAC. This could be achieved if inhalation anaesthesia was used to produce "insensibility" in combination with a regional technique or a local anaesthetic block.

If it is agreed that there are advantages in using desflurane in this particular group of patients, cost becomes an important consideration. Taking the example of a 3-kg infant using a fresh gas flow of 1300 ml min^{-1} [13], 1 h of desflurane used at 1 MAC for an infant is estimated to cost £5.47 per hour compared with £1.91 for 1 MAC of isoflurane. This moderate increase in anaesthesia cost becomes irrelevant if the use of desflurane enables postoperative extubation and thus avoids intensive care admission.

References

1. Steward DJ. Preterm infants are more prone to complications following minor surgery than are term infants. *Anesthesiology* 1982; **56**: 304–306.
2. Krane EJ, Haberkern CM, Jacobson LE. Postoperative apnea, bradycardia, and oxygen desaturation in formerly premature infants: Prospective comparison of spinal and general anesthesia. *Anesthesia and Analgesia* 1995; **80**: 7–13.
3. Eger EI II. Partition coefficients of I653 in human blood, saline and olive oil. *Anesthesia and Analgesia* 1987; **66**: 971–973.
4. Cromwell TH, Eger EI II, Stevens WC, Dolan WM. Forane uptake, excretion, and blood solubility in man. *Anesthesiology* 1971; **35**: 401–408.
5. Taylor RH, Lerman J. Induction, maintenance and recovery characteristics of desflurane in infants and children. *Canadian Journal of Anaesthesia* 1992; **39**: 6–13.
6. Talor RH, Lerman J. Minimum alveolar concentration of desflurane and hemodynamic responses in neonates, infants and children. *Anesthesiology* 1991; **75**: 975–979.
7. Cameron CB, Robinson S, Gregory GA. The minimum alveolar concentration of isoflurane in children. *Anesthesia and Analgesia* 1984; **63**: 418–420.
8. de Swiet M, Fayers P, Shinebourne EA. Blood pressure in the first 10 years of life: the Brompton study. *British Medical Journal* 1992; **304**: 23–26.
9. Altman DG. Statistics and ethics in medical research. III. How large a sample? *British Medical Journal* 1980; **281**: 1336–1338.
10. Hatch DJ, Sumner E. Neonatal physiology and anaesthesia. In: Sumner E, Hatch DJ, eds. *Textbook of Paediatric Anaesthetic Practice*. London: Baillière Tindall, 1989; 265.
11. Welborn LG, Ramirez N, Oh TH, Ruttimann UE, Fink R, Guzzetta P, Epstein BS. Postanesthetic apnea and periodic breathing in infants. *Anesthesiology* 1986; **65**: 658–661.
12. Kurth CD, Spitzer AR, Broennle AK, Downes JJ. Postoperative apnea in preterm infants. *Anesthesiology* 1987; **66**: 483–488.
13. Rose DK, Froese AB. Regulation of Pa_{CO_2} during controlled ventilation of children with a T-piece. *Canadian Anaesthetists Society Journal* 1979; **26**: 104.

British Journal of Anaesthesia 1996; **76**: 365–368

Perioperative changes in α_1-acid glycoprotein concentrations in infants undergoing major surgery

P. D. BOOKER, C. TAYLOR AND G. SABA

Summary

α_1-Acid glycoprotein (AAG) is an acute phase protein that is responsible for binding basic drugs such as bupivacaine. In order to determine how AAG concentrations change in response to surgical stress, arterial blood samples were obtained from 50 infants undergoing major surgery, at induction of anaesthesia and daily for the next 7 days. AAG concentrations were measured using a rate nephelometric technique. The overall mean preoperative AAG concentration was 0.38 (SD 0.16) mg ml^{-1}, although concentrations were significantly greater in infants undergoing urgent surgery compared with those undergoing elective surgery ($P = 0.02$). There were no significant correlations between gestational or postnatal age and preoperative AAG concentration. Mean AAG concentrations increased to 0.76 (0.18) mg ml^{-1} by day 4 after surgery and stayed at that concentration thereafter. Infants with preoperative AAG concentrations < 0.38 mg ml^{-1} showed a greater percentage increase in postoperative AAG concentrations than did infants with preoperative AAG concentrations > 0.38 mg ml^{-1} ($P = 0.001$). We conclude that preoperative measurement of AAG may identify those infants most at risk of drug toxicity in the early postoperative period. (*Br. J. Anaesth.* 1996; **76**: 365–368)

Key words
Anaesthesia, paediatric. Protein, α_1-acid glycoprotein. Infants.

Plasma protein binding of drugs may have significant pharmacodynamic implications, because it is the unbound moiety that diffuses most readily across biological membranes, reaches receptor sites to produce pharmacological effects and is available for elimination from the body. Although albumin (ALB) has a greater binding capacity than α_1-acid glycoprotein (AAG), AAG has much greater drug affinity for drugs with pK_a values of 8 or more, and binding of basic drugs decreases in AAG-deficient plasma [1, 2]. However, changes in protein binding are only important clinically for drugs which are highly bound to plasma proteins, such as bupivacaine (96% bound) [3], sufentanil and alfentanil (both 92% bound) [4]. If variations occur in the plasma concentrations of AAG, then the free plasma concentration of the bound drug can vary considerably, whereas the total concentration of the drug in plasma is only slightly affected.

The normal average plasma concentration of AAG in a healthy adult is 77 mg ml^{-1}, although there is great individual variation [5]. Many physiological factors influence AAG concentrations, including time of day [6], age [7, 8], sex [5, 7], pain [9] and nutritional status [10, 11]. Newborn infants may have very low plasma concentrations of AAG (and ALB) which tend to increase with age, to reach adult values by about 10 months of age [12]. Moreover, AAG is one of several plasma proteins synthesized by the liver; its concentration changes in response to various stressful stimuli, such as trauma [13], burns [14], malignancy [15] or infection [12, 16]. Thus the concentrations of "acute phase proteins" would be expected to change after major surgery, as has been shown in adults [17, 18], although this has not been confirmed in infants or children.

The latency period and extent of the change in AAG concentrations may be expected to have significant clinical implications for infants undergoing major surgery, as these patients are most likely to be receiving infusions of local anaesthetic or opioids in the immediate postoperative period. Therefore, in an attempt to define further the changes in plasma protein concentrations that may occur in this group of patients, we measured AAG plasma concentrations in infants requiring major surgery, both before and daily for 7 days after surgery.

Patients and methods

We obtained local Ethics Committee approval and written, informed consent from the parents of 116 infants, aged 3–200 postnatal days, presenting for major abdominal, thoracic or cardiac surgery and expected to require prolonged postoperative intensive care. Patients with tumours or suspected infection were excluded. The clinical notes were examined to determine maturity at birth and the gestational age of each infant at the time of surgery was calculated accordingly.

After induction of anaesthesia, a 0.5-ml arterial blood sample was obtained. This sampling was repeated every morning for the next 7 days or until

---

P. D. BOOKER, FRCA, C. TAYLOR*, FRCA, G. SABA, FRCA, Department of Paediatric Anaesthesia, Royal Liverpool Children's NHS Trust, Eaton Road, Liverpool L12 2AP.
Accepted for publication: October 12, 1995.
*Present address: Department of Anaesthesia, Morriston Hospital NHS Trust, Morriston, Swansea SA6 6NL.

the arterial cannula was removed, whichever was sooner. We obtained all eight samples from 50 infants and blood was analysed for AAG using a rate nephelometric immunoassay technique (Beckman Array 360 System), which has a sensitivity of ±3%. All patients were given peroperative analgesia using opioids, local anaesthetic drugs, or both; infusions of opioids were continued into the postoperative period for as long as was deemed clinically appropriate.

Daily full blood counts, bacteriological cultures and measurement of C-reactive protein (CRP) were performed routinely. If there was any clinical suspicion of infection together with a $>50\%$ increase in leucocyte count or CRP, or $>50\%$ decrease in platelet count after the second post-operative day, or positive bacteriological cultures, or both, the AAG data for that patient were subsequently discarded. Routine biochemical monitoring of these patients included hepatic function tests every 2 days, or more frequently if indicated clinically. In addition to glucose infusions to maintain normal calorie intake, all patients were given protein supplementation either enterally (formula or breast milk) or i.v. (Primene 10%, Clintec) by day 3 after surgery, according to our normal clinical practice.

Two sample *t* tests were used to compare mean AAG concentrations between male and female infants, between infants with preoperative AAG concentrations < 0.38 mg ml^{-1} and infants with preoperative AAG concentrations $\geqslant 0.38$ mg ml^{-1}, and between infants requiring urgent and elective surgery. Kendall's tau-b rank correlation coefficient was used to assess associations between age and preoperative AAG concentrations.

Results

The mean preoperative plasma AAG concentration was 0.38 (SD 0.16) mg ml^{-1}, although there was wide inter-patient variation (range 0.07–0.78 mg ml^{-1}). Figure 1 shows the poor correlation between pre-operative AAG concentration and gestational age (correlation coefficient, $r = 0.09$; $P = 0.09$); a similar correlation existed for AAG concentration and postnatal age ($r = 0.07$; $P = 0.14$).

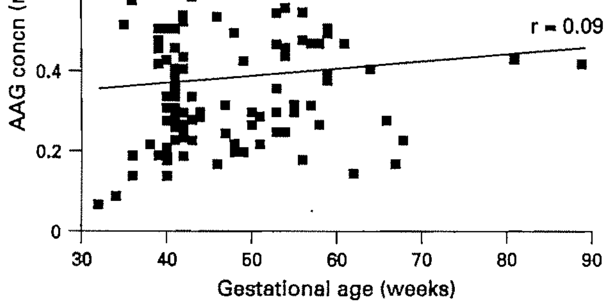


Figure 1 Individual plasma concentrations of α_1-acid glycoprotein (AAG) in 116 infants, obtained before operation, plotted against gestational age.

Table 1 Gestational age, postnatal age and preoperative plasma protein concentrations (mean (SD or range)) in males and females. AAG = α_1-acid glycoprotein

	Male ($n = 64$)	Female ($n = 52$)	*P*
Gestational age (weeks)	45.5 (34–71)	49.6 (32–89)	0.03
Postnatal age (weeks)	6.69 (0.0–31.4)	10.4 (0.0–51.0)	0.05
AAG concn (mg ml^{-1})	0.42 (0.17)	0.33 (0.14)	0.002

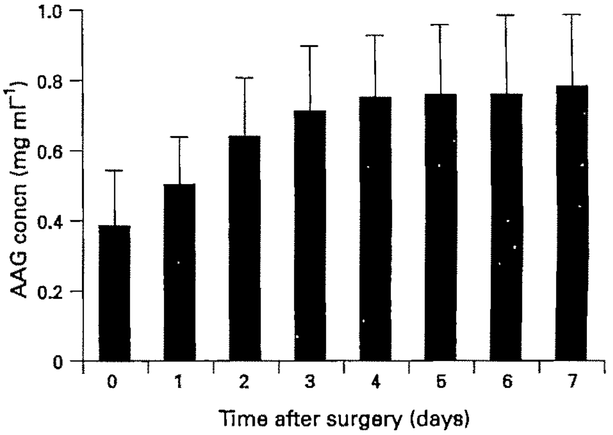


Figure 2 Mean (SD) plasma concentrations of α_1-acid glycoprotein before ($n = 116$) and after ($n = 50$) major surgery in young infants.

There was a significant difference between the sexes in mean AAG concentrations ($P = 0.002$) (table 1). Female infants had a mean gestational age of 49.6 (11.1) weeks compared with males who had a mean gestational age of 45.5 (8.0) weeks ($P = 0.03$). There were similar differences in postnatal age between the sexes ($P = 0.05$).

There was an increase in mean AAG concentration, to 0.76 (0.18) mg ml^{-1}, by day 4. Thereafter, AAG concentrations remained at or around this elevated concentration for the duration of the study (fig. 2).

Patients ($n = 29$) in whom preoperative values of AAG were less than the mean (0.38 mg ml^{-1}) were compared with those patients ($n = 21$) in whom preoperative AAG values were at or greater than the mean value (obtained from 116 infants). These data show that those infants with low preoperative AAG values had a much greater increase in postoperative values than did the group with higher preoperative AAG values ($P = 0.001$) (table 2).

Table 3 shows the mean perioperative AAG concentrations in infants requiring urgent compared with those requiring general surgery; there was a significant difference between the groups in pre-operative values, despite the gestational age in the elective surgery group being significantly older than in the urgent surgery group. AAG concentrations after surgery did not differ significantly between the

Table 2 Differences in mean AAG concentrations between postoperative values and preoperative concentration expressed as percentage change (SD). Patients ($n = 29$) in whom preoperative values were less than the mean (0.38 mg ml^{-1}) (group A) were compared with those patients ($n = 21$) in whom preoperative values were at or greater than the mean (group B)

Day after surgery	% Change in group A	% Change in group B	*P*
1	85.5 (50.3)	27.9 (19.1)	0.001
2	167.1 (97.1)	45.5 (29.0)	0.001
3	209.1 (109.5)	57.1 (35.9)	0.001
4	198.4 (94.2)	60.3 (32.7)	0.001
5	241.1 (114.3)	74.5 (57.7)	0.002
6	230.7 (123.7)	80.2 (69.5)	0.017
7	262.2 (121.2)	83.5 (62.9)	0.013

groups at any time. There were no significant differences in gestational age or perioperative AAG concentrations between infants requiring cardiac and those requiring abdominal surgery.

Discussion

The therapeutic safety margin for many analgesic drugs is reduced in infancy, because of increased sensitivity to the respiratory depressant effects of opioids [19], immature drug elimination pathways [19, 20] and, as we have now confirmed indirectly, a reduction in the plasma protein binding of drugs [21, 22]. Although the provision of postoperative analgesia in this age group is receiving increasing attention [23, 24], there are few data on plasma protein binding of analgesic drugs in infancy.

This study has confirmed previous neonatal studies [12, 16] showing that mean plasma concentrations of AAG in infants are about 50% of those in healthy adults. The large inter-patient variation seen in AAG concentrations reflects not only general individual variation but also the diversity in preoperative "stress". We compared preoperative AAG concentrations in infants who required elective surgery with those requiring urgent surgery, and found a significantly lower concentration in the elective surgical group ($P = 0.02$). Although these latter infants were significantly older ($P = 0.001$), a factor which should have increased the AAG concentration, they were less sick and presumably less "stressed" than those infants requiring urgent surgery. As would be expected, the type of surgery had no significant effect on preoperative AAG concentrations.

Previous studies have shown that AAG concentrations increase with increasing gestational age between 28 weeks and term [12, 16, 25], reaching adult concentrations by about 10–12 months of age [12, 26]. Our results agree with the previous findings of Bienvenu and colleagues [12] who found that, from the third postnatal day, the influence of gestational age on AAG concentrations was insignificant. Our finding of a significant difference in preoperative AAG concentrations between males and females is in contrast with previous neonatal [16] and adult [4] studies which showed little difference between the sexes, but supports a larger adult study [5]. This apparent anomaly may be explained by one neonatal study [25] which found no significant difference between the sexes at birth but a difference after the fourth day of life. Although our females were significantly older than the males, they had significantly lower mean preoperative AAG concentrations; this age difference in our male and female groups thus makes the AAG concentration difference between the sexes meaningful.

We have shown that most infants had an increase in AAG concentration in response to major surgical trauma, and by 4 days after surgery the AAG concentrations had doubled to 0.76 mg ml^{-1}, irrespective of the type or urgency of the surgery. Infants with preoperative AAG concentrations > 0.38 mg ml^{-1} showed a smaller percentage increase in the postoperative period than those infants with preoperative AAG concentrations < 0.38 mg ml^{-1}. We postulate that the higher preoperative values in the more stressed infants undergoing urgent surgery, reflects a sharp increase in hepatic AAG production that occurred before operation. The rate of increase in AAG production thereafter was consequently less than in those individuals who began to increase their hepatic AAG production only in response to surgical stress. However, the sickest neonates, particularly those with clinically and biochemically significant signs of hepatic dysfunction, exhibited little change and concentrations remained less than 0.5 mg ml^{-1}, often decreasing from their preoperative value. Low numbers of such patients and the lack of a widely accepted objective scoring system precluded separate

Table 3 Gestational age (mean (range)) and perioperative AAG concentrations (mean (SD) mg ml^{-1}) of infants requiring elective surgery compared with those requiring urgent surgery and in infants requiring abdominal surgery compared with those requiring cardiac surgery. AAG = α_1-acid glycoprotein

	Elective surgery ($n = 89$)	Urgent surgery ($n = 27$)	*P*	Cardiac surgery ($n = 90$)	General surgery ($n = 26$)	*P*
Age (weeks)	49.1 (35–89)	40.9 (32–61)	0.001	48.1 (36–89)	44.5 (32–81)	0.16
AAG concn						
Preop.	0.37 (0.18)	0.47 (0.19)	0.02	0.38 (0.16)	0.36 (0.20)	0.69
Day 1	0.50 (0.12)	0.58 (0.20)	0.19	0.52 (0.13)	0.54 (0.22)	0.82
Day 2	0.63 (0.17)	0.71 (0.21)	0.23	0.64 (0.17)	0.73 (0.25)	0.43
Day 3	0.75 (0.18)	0.66 (0.20)	0.21	0.74 (0.18)	0.68 (0.24)	0.38
Day 4	0.76 (0.18)	0.76 (0.20)	0.97	0.75 (0.18)	0.87 (0.25)	0.64
Day 5	0.78 (0.18)	0.78 (0.19)	0.99	0.79 (0.19)	0.77 (0.24)	0.27
Day 6	0.80 (0.20)	0.78 (0.21)	0.38	0.78 (0.22)	0.74 (0.20)	0.34
Day 7	0.83 (0.21)	0.75 (0.16)	0.22	0.81 (0.22)	0.78 (0.19)	0.23

analyses of patients on the basis of severity of sickness in the postoperative period. However, one adult study has suggested that AAG concentrations decrease in proportion to the degree of hepatic dysfunction [27].

We suggest that preoperative measurement of AAG concentration should be performed in all infants undergoing elective major surgery who are expected to receive prolonged bupivacaine infusions in the postoperative period. Bupivacaine toxicity is not unknown in this age group [28] and this phenomenon may be related to low plasma protein concentrations. The maximum bupivacaine dose should be reduced in infants with preoperative AAG concentrations < 0.3 mg ml^{-1} and in infants with significant hepatic dysfunction.

Acknowledgement

Financial support for the study was given by the Royal Liverpool Children's NHS Trust Research Fund.

References

1. Pike E, Kierulf P, Skuterud B, Bredesen JE, Lunde PKM. Drug binding in sera deficient in lipoproteins, albumin or orosomucoid. *British Journal of Clinical Pharmacology* 1983; **16**: 233–239.
2. Hynynen M, Hynninen M, Soini H, Neuvonen PJ, Heinonen J. Plasma concentration and protein binding of alfentanil during high-dose infusion for cardiac surgery. *British Journal of Anaesthesia* 1994; **72**: 571–576.
3. Denson D, Coyle D, Thompson G, Myers J. Alpha$_1$-acid glycoprotein and albumin in human serum bupivacaine binding. *Clinical Pharmacology and Therapeutics* 1984; **35**: 409–415.
4. Meuldermans WEG, Hurkmans RMA, Heykants JJP. Plasma protein binding and distribution of fentanyl, sufentanil, alfentanil and lofentanil in blood. *Archives Intensivie Pharmacodynamie* 1982; **257**: 4–19.
5. Blain PG, Mucklow JC, Rawlins MD, Roberts DF, Routledge PA, Shand DG. Determinants of plasma α_1-acid glycoprotein concentrations in health. *British Journal of Clinical Pharmacology* 1986; **12**: 500–502.
6. Yost RL, Devane CL. Diurnal variation of alpha-1-acid glycoprotein concentration in normal volunteers. *Journal of Pharmaceutical Science* 1985; **74**: 777–779.
7. Verbeeck RK, Cardinal J-A, Wallace SM. Effect of age and sex on the plasma binding of acidic and basic drugs. *European Journal of Clinical Pharmacology* 1984; **27**: 91–97.
8. LeDez KM, Swartz J, Strong A, Burrow FA, Lerman J. The effect of age on the serum concentration of alpha-1-acid glycoprotein in newborns, infants and children. *Anesthesiology* 1986; **65**: A421.
9. Fukui T, Hameroff SR, Gandolfi J. Alpha-1-acid glycoprotein and beta-endorphin alterations in chronic pain patients. *Anesthesiology* 1984; **60**: 494–496.
10. Jagadeesan V, Krishnaswamy K. Drug binding in the undernourished: a study of the binding of propranolol to α_1-acid glycoprotein. *European Journal of Clinical Pharmacology* 1985; **27**: 657–659.
11. Benedek IH, Fisk WD III, Griffin WO, Bell RM, Blouin RA, McNamara PJ. Serum α_1-acid glycoprotein and the binding of drugs in obesity. *British Journal of Clinical Pharmacology* 1983; **16**: 751–754.
12. Bienvenu J, Sann L, Bienvenu F, Lahet C, Divry P, Cotte J, Bethenod M. Laser nephelometry of orosomucoid in serum of newborns: reference levels and relation to bacterial infections. *Clinical Chemistry* 1981; **27**: 721–726.
13. Edwards DJ, Lalka D, Cerra Fl, Slaughter RL. Alpha$_1$-acid glycoprotein concentration and protein binding in trauma. *Clinical Pharmacology and Therapeutics* 1982; **31**: 62–67.
14. Macfie AG, Magides AD, Reilly CS. Disposition of alfentanil in burns patients. *British Journal of Anaesthesia* 1992; **69**: 447–450.
15. Chio LF, Oon CJ. Changes in serum alpha$_1$ antitrypsin, alpha$_1$-acid glycoprotein and beta$_2$ glycoprotein I in patients with malignant hepatocellular carcinoma. *Cancer* 1979; **43**: 596–604.
16. Philip AGS, Hewitt JR. α_1-Acid glycoprotein in the neonate with and without infection. *Biology of the Neonate* 1983; **43**: 118–124.
17. Aronsen K-F, Ekelund G, Kindmark C-O, Laurell C-B. Sequential changes of plasma proteins after surgical trauma. *Scandinavian Journal of Clinical Investigation* 1972; **29**: 127–136.
18. Colley CM, Fleck A, Goode AW, Muller BR, Myers MA. Early time course of the acute phase protein response in man. *Journal of Clinical Pathology* 1983; **36**: 203–207.
19. Koehntop DE, Rodman JH, Brundage DM, Hegland MG. Pharmacokinetics of fentanyl in neonates. *Anesthesia and Analgesia* 1986; **65**: 227–232.
20. Choonara IA, McKay P, Hain R, Rane A. Morphine metabolism in children. *British Journal of Clinical Pharmacology* 1989; **28**: 599–604.
21. Meistelman C, Benhamou D, Barre J, Levron J-C, Mahe V, Mazoit X, Ecoffey C. Effects of age on plasma protein binding of sufentanil. *Anesthesiology* 1990; **72**: 470–473.
22. Mazoit JX, Denson DD, Samii K. Pharmacokinetics of bupivacaine following caudal anesthesia in infants. *Anesthesiology* 1988; **68**: 387–391.
23. Anand KJS, McGrath PJ, eds. *Pain in Neonates*. London: Elsevier, 1993.
24. Anonymous. Treating moderate and severe pain in infants. *Drugs and Therapeutics Bulletin* 1994; **32**: 21–24.
25. Boichot P, Schirrer J, Meget A, Raffi A. L'orosomucoïde à la période néonatale. Etude chez le nouveau-né sain et le nouveau-né infecté. *Pédiatrie* 1980; **35**: 577–588.
26. Pacifici GM, Viani A, Taddeucci-Brunelli G, Rizzo G, Carrai M, Schulz H-U. Effects of development, aging and renal and hepatic insufficiency as well as hemodialysis on the plasma concentrations of albumin and α_1-acid glycoprotein: implications for binding of drugs. *Therapeutic Drug Monitoring* 1986; **8**: 259–263.
27. Barry M, Keeling PWN, Weir D, Feely J. Severity of cirrhosis and the relationship of α_1-acid glycoprotein concentration to plasma protein binding of lidocaine. *Clinical Pharmacology and Therapeutics* 1990; **47**: 366–370.
28. Larsson BA, Olsson GL, Lonnqvist PA. Plasma concentrations of bupivacaine in young infants after continuous epidural infusion. *Paediatric Anaesthesia* 1994; **4**: 159–162.

British Journal of Anaesthesia 1996; **76**: 369–373

Changes in chest wall compartment volumes on induction of anaesthesia with eltanolone, propofol and thiopentone†

H. J. SPENS, G. B. DRUMMOND AND P. K. WRAITH

Summary

Changes in the expiratory dimensions of the rib cage and abdomen on induction of anaesthesia with eltanolone, propofol and thiopentone were measured in 76 patients using respiratory inductance bands. Calibration of the respiratory inductance plethysmograph was by simultaneous flow measurement with a pneumotachograph. Movement of the vertebral column was restrained with a rigid mattress to allow volume change to be estimated more accurately from rib cage and abdominal dimensions. Rib cage volumes decreased by a median of 125 ml, while the median change in the abdominal compartment was 0. These findings suggest that a reduction in rib cage volume may contribute to the decrease in functional residual capacity after induction of anaesthesia, but that changes in the diaphragmatic–abdominal compartment are not important. (*Br. J. Anaesth.* 1996; **76**: 369–373)

Key words

Lung, volume. Lung, functional residual capacity. Muscle respiratory. Anaesthetics i.v., propofol. Anaesthetics i.v., thiopentone. Anaesthetics i.v., eltanolone.

It is generally accepted that induction of anaesthesia in supine humans is associated with a reduction in functional residual capacity (FRC) of approximately 20% [1]. Changes in chest wall configuration are probably responsible, either by inward movement of the rib cage or by cephalad movement of the diaphragm [2].

Previous studies of changes in chest wall dimensions at induction of anaesthesia have reported inconsistent results. Rib cage dimensions decreased in some studies but not in others. Abdominal dimensional changes, used to infer movement of the diaphragm, have been even less conclusive [3–7].

Possible reasons for these discrepancies include small sample size and different measuring techniques used, but another potential source of error is spinal movement. Flexion or extension of the spine changes rib cage and abdominal dimensions without a change in lung volume [8]. Spinal movement occurs on induction of anaesthesia [2] and invalidates the assumption of two degrees of freedom implicit in the Konno and Mead analysis of chest wall movement [9]. A more recent study [10] measured dimensional changes in rib cage and abdomen while preventing spinal movement, and reported a reduction in chest wall dimensions on induction of anaesthesia, but no attempt was made to assess possible volume changes.

Therefore, we have measured the changes in the dimensions of the rib cage and abdomen on induction of anaesthesia in a large number of patients while firmly supporting the spine, and estimated the volume changes and contribution of the rib cage and diaphragmatic–abdominal compartments to the reduction in FRC that occurs on induction of anaesthesia. As a previous study using this method [11] reported different results for thiopentone compared with propofol, we have compared three i.v. induction agents.

Patients and methods

All patients were part of a larger study on the ventilatory effects of eltanolone compared with propofol and thiopentone. This study was approved by the local Ethics Committee, and informed consent was obtained from each patient.

We recruited 76 patients, aged 18–65 yr, of both sexes, ASA I or II, undergoing elective surgery. We excluded patients who were obese (more than 50% above ideal weight for height, Metropolitan Life Insurance Company scale), pregnant, had significant respiratory disease or anaesthetic drug allergy or who had abused alcohol or other substances. Patients received no premedication and were allocated randomly to receive eltanolone 0.75 mg kg^{-1}, propofol 2.5 mg kg^{-1} or thiopentone 4 mg kg^{-1} for induction of anaesthesia. These doses have been shown to be approximately equipotent [12, 13].

On arrival in the anaesthetic room, an i.v. cannula was inserted and patients were positioned on a "Vac-Pac" mattress (Howmedica). This is filled with polystyrene beads and thus conforms exactly to the curvature of the spine. Air was then evacuated from the mattress causing it to become rigid, preventing spinal movement.

Respiratory inductance bands were placed around the chest immediately below the axillae, and around the abdomen, at the level of the umbilicus. These

---

H. J. SPENS, MB, CHB, FRCA, G. B. DRUMMOND, MA, MB, CHB, FRCA, University Department of Anaesthetics, Royal Infirmary, Edinburgh EH3 9YW. P. K. WRAITH, PHD, University Department of Medical Physics, Western General Hospital, Edinburgh EH4 2XU. Accepted for publication: September 13, 1995.

†Presented in part at the Anaesthetic Research Society, London Meeting, November 11–12, 1994 (*British Journal of Anaesthesia* 1995; 74: 472P).

were connected to a respiratory inductance plethysmograph (RIP), made by the Edinburgh University Department of Medical Physics. The signal output was AC-coupled with a time constant of approximately 2 min. The resulting signals, which represent changes in cross-sectional area of the rib cage and abdomen with respiration and which are accepted as proportional to compartment volume, were recorded on a lap-top computer using the commercial respiratory monitoring software Cardas (version 2.07 advanced, Oxcams, Oxford), running in MS-DOS (version 6.20).

Patients breathed 35% oxygen from a T-piece through a screen pneumotachograph (F100L, Mercury Electronics) and a tight fitting face mask with a wide pneumatic seal (Downs CPAP mask No. 9002, Vital Signs Inc., NJ, USA), held in place bimanually by the anaesthetist. The pneumotachograph was connected to a differential pressure transducer (0–10 mm H_2O, Furness) and the resulting flow signal was also recorded on the computer. The system was calibrated in the laboratory using a series RT200 calibration analyser (Timeter Instrument Corporation, Missouri, USA) and the voltage output was linear against an input flow of up to 40 litre min^{-1}. Immediately before each study, calibration was checked against a flowmeter (whose accuracy had also been verified in the laboratory), and was considered acceptable if the error was less than ±5%.

After a period of 3–5 min of stable breathing, the induction agent was administered over 30 s and RIP and flow signals were recorded for another 4 min. The jaw was supported gently by the anaesthetist to prevent upper airways obstruction. No other anaesthetic agent was administered during this time. The moment of loss of consciousness was noted from when the patient dropped a metal rod held between thumb and index finger. After completion of this study period, anaesthesia was continued as appropriate for clinical management.

The RIP signals (mV) were calibrated against the integrated flow signal (ml) by a multiple linear regression technique [14], using a stable 30-s period before induction of anaesthesia, and the volume–motion coefficients (ml mV^{-1}) for the rib cage and abdomen were calculated. The end-expiratory positions of the rib cage and abdomen were taken from a line fitted by eye on the RIP trace over approximately 1 min immediately before induction (baseline) and from the point of maximal change after loss of consciousness, and the difference (mV) was measured as shown in figure 1. These changes were then multiplied by their respective volume–motion coefficients to estimate the volume change of each compartment on induction of anaesthesia for each patient.

The consistency of the RIP calibration method was assessed as follows. Ten sets of patient data were selected randomly, and from each of these sets of data the 10 breaths immediately before the 30-s period actually used for calibration were analysed. The percentage difference between the RIP derived tidal volume (V_T) and the pneumotachograph derived V_T was then calculated for each of these breaths.

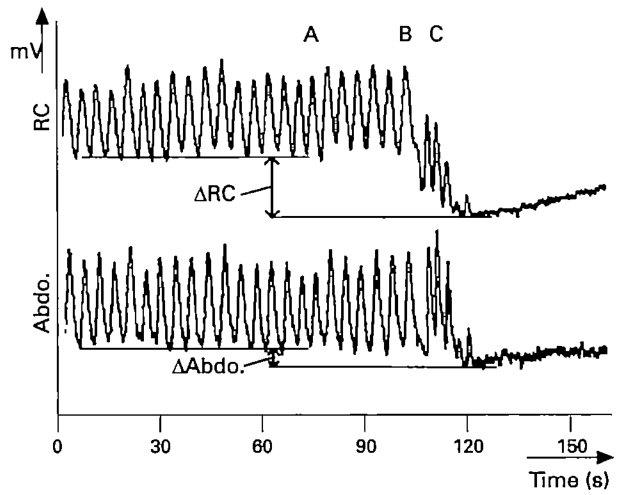


Figure 1 Typical respiratory inductance plethysmograph recording. A and B = start and end of administration of induction agent, respectively; C = moment of loss of consciousness. ΔRC and ΔAbdo. = measured changes in the end-expiratory position of the rib cage and abdomen after induction.

Data were analysed using the Minitab statistical package (release 8.2), in MS-DOS (version 6.20). Changes in chest wall volumes from baseline were tested using the Wilcoxon test and between-group changes were compared with the Kruskal–Wallis test. $P < 0.05$ was considered significant.

Results

Of the original 76 patients studied, results were available for analysis from 59. Reasons for the missing data are shown in table 1. The characteristics of those included are summarized in table 2. There were more males in the propofol group and more females in the thiopentone group than in the eltanolone group, with a corresponding bias in weight and height.

Table 1 Reasons for exclusion of data from analysis

	No. missing
Equipment problems	7
Study violation	2
Movement artefact	4
Airway obstruction	1
Unstable baseline data	2
Operation cancelled	1

Table 2 Patient characteristics (median (quartile values) [range])

	Eltanolone ($n = 19$)	Propofol ($n = 20$)	Thiopentone ($n = 20$)
Age (yr)	40 (32, 43) [18–58]	34 (30, 44) [22–54]	38 (26, 46) [20–64]
Height (cm)	170 (166, 175)	178 (172, 181)	167 (161, 173)
Weight (kg)	73 (63, 76)	73 (66, 79)	65 (56, 70)
Sex (M:F)	9:10	14:6	5:15

Table 3 Changes in the volumes of the rib cage (ΔRC) and abdominal (ΔAb) compartments on induction of anaesthesia (median (quartile values)). ΔRC+ΔAb = median of the overall changes in chest wall volume measured from the individual totals of ΔRC and ΔAb

	ΔRC (ml)	ΔAb (ml)	ΔRC+ΔAb (ml)
Eltanolone ($n = 19$)	−83 (−232, −17)	0 (−73, 94)	−103 (−237, −14)
Propofol ($n = 20$)	−307 (−408, −88)	0 (−14, 31)	−299 (−448, −34)
Thiopentone ($n = 20$)	−121 (−205, −47)	29 (−28, 63)	−160 (−325, −39)
All patients ($n = 59$)	−125 (−319, −39)	0 (−35, 71)	−136 (−353, −33)

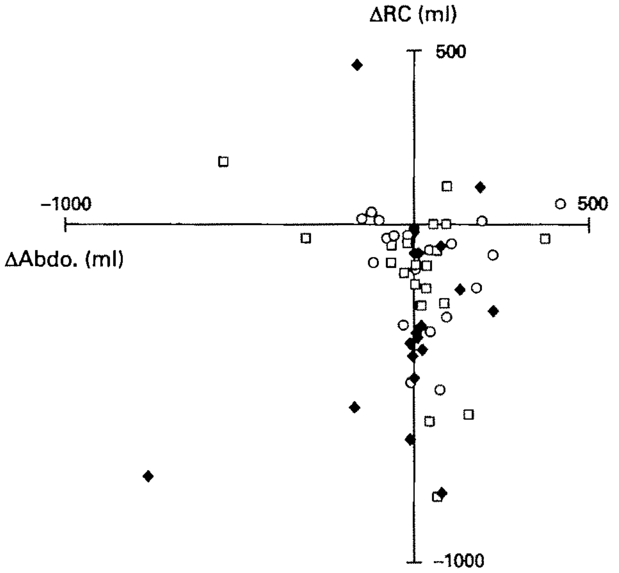


Figure 2 Change in rib cage volume (ΔRC) *vs* change in abdominal volume (ΔAbdo.) for each patient in the eltanolone (○), propofol (◆) and thiopentone (□) groups.

The consistency of the RIP calibration showed that the mean overall RIP derived V_T was 3.8 % less than the mean pneumotachograph derived V_T. Sixty-two percent of values of RIP V_T lay within ±10 % of pneumotachograph V_T, and 92 % were within ±20 %.

Table 3 shows the median changes in the volume of the rib cage and abdominal compartments, and the total volume change of the chest wall measured from the individual totals of rib cage and abdominal volume changes. In general, the changes in compartment volume began approximately 30 s after the start of administration of the induction agent and developed over approximately 30 s. Loss of consciousness occurred at a mean of 45 s after the start of injection. The decrease in rib cage volume in patients receiving propofol was greater than in the two other groups, but a Kruskal–Wallis test indicated that the groups were not significantly different ($P = 0.1$). Other differences between groups were even less marked. Because there were no significant differences between the three groups, the changes in compartmental volumes were pooled and analysed together.

Rib cage volumes increased in nine subjects and decreased in 50, with a median overall reduction of 125 ml. Abdominal volumes increased in 29, decreased in 22, and did not change in eight (median change = 0). The median overall reduction in chest wall volume, measured from the total change in rib cage volume and abdominal volume, was 136 ml. The changes in rib cage volume and chest wall volume were significantly different from 0 ($P < 0.05$), but the change in abdominal volume was not (median change 0, interquartile range −35 to 71 ml). The commonest pattern of change was a reduction in rib cage volume and a smaller increase in abdominal volume (fig. 2).

Discussion

These results confirm that induction of anaesthesia with i.v. agents is associated with a decrease in chest wall volume. However, the magnitude of this change was small, with a median reduction of only 136 ml. A reduction in the volume enclosed by the rib cage was almost entirely responsible for the overall volume change, with a median change in abdominal volume of 0. Our results were absolute values but previous studies have often expressed data as a percentage of FRC. We did not measure FRC and did not attempt to relate the changes we found to a predicted lung volume.

A potential source of error in any study of this type is calibration of RIP. In this study a multiple linear regression technique (MLR) was used which depends on a natural breath-to-breath variation in the contribution of rib cage and abdominal motion to respired volume. Unlike the isovolume method [9] MLR does not require patient co-operation to learn a difficult respiratory manoeuvre, or a change in posture, as used in other methods [15], which may in itself alter the volume–motion coefficients of rib cage and abdomen [16, 17]. However, the statistical association of rib cage and abdominal movement can make the predictive value of one component of the MLR less relevant.

The validation results in the present study showed that the precision and accuracy of our calibration technique were comparable with those reported by other workers, using a variety of calibration methods, when posture is not changed [18–20]. Possible problems with our method include the fact that we used a single calibration period rather than averaging the volume–motion coefficients from several, and that we used the whole respiratory cycle for the MLR analysis rather than only the more stable middle portion of inspiration. However, for the purposes of the present research, we feel our method is adequate.

There may also have been other sources of error such as unrecognized mask leaks. To minimize this we used a face mask with a wide pneumatic rim, applied water-soluble jelly if facial stubble was present, and held the mask in place with two hands allowing manual detection of escaping gas. Use of a carbon dioxide monitor in some patients showed a normal waveform with normal end-tidal values, confirming our belief that significant gas leaks did not occur.

The median reduction in chest wall volume of 136 ml after i.v. induction of anaesthesia in this study was remarkably small. Other workers, using helium dilution, nitrogen washout and body plethysmography techniques to measure FRC have reported larger reductions, from 300 to 700 ml [3, 21–24]. Many factors may explain these differences; first, as we were using an AC-coupled system, the relationship between the time constant of our RIP (2 min) and the time course of the change in end-expiratory compartment volume (30 s) may have resulted in a small underestimate of the volume changes. A longer time constant would reduce this error, but would increase the time needed to reach a steady baseline. Second, it has been postulated that increases in the volume of blood and tissue in the thoracic cavity may occur on induction of anaesthesia. This may decrease the volume of intrathoracic gas and hence FRC without affecting rib cage and abdominal dimensions. However, in awake subjects, splints around the lower limbs decrease the volume of intrathoracic gas but increase chest wall dimensions [25], and recent work using CT scanning showed a reduction in chest wall volume on induction of anaesthesia but no change in intrathoracic blood or tissue volume [2].

Alternatively, the third degree of freedom of movement of the chest wall [8] may be responsible for the difference in magnitude of FRC reduction between our results and those of other workers. Unlike other investigators we intended to eliminate this freedom of movement by firmly supporting the spine. It has been shown [2] that induction of anaesthesia can result in an increase in the curvature of the thoracic spine. The Vac-Pac mattress may eliminate skeletal movement in these circumstances [26]. Therefore, in other studies of FRC a change in thoracic flexion could cause an additional decrease in intrathoracic gas, which did not occur in our patients. Other possible causes of this discrepancy relate to the timing of FRC measurements. In studies using helium dilution, nitrogen clearance or body plethysmography to measure FRC, some time elapsed between induction of anaesthesia and FRC measurement. Over 15 min, FRC may be reduced in conscious subjects by breathing oxygen-enriched gas mixtures [27] and this effect could contribute to the greater decreases found in previous studies. A delay in measurement of FRC may also allow onset of phasic expiratory activity in the abdominal muscles [2] which could also reduce FRC. This may not have been seen in this study as measurements were made immediately after induction, often during a period of apnoea. This postulate is supported by studies measuring changes in end-expiratory lung volume with spirometry immediately after induction [28, 29], where smaller reductions in FRC of only 243 and 188 ml were found, closer to our results.

A final possible explanation for these differences might be that our study, and others reporting FRC changes of a similar magnitude [28, 29], used face-mask anaesthesia, while those workers who found larger reductions in FRC used tracheal tubes to maintain the airway. This may affect FRC. Bickler, Dueck and Prutow [30] found only a 3.5 % reduction in FRC in patients breathing via a face mask, compared with a 22 % reduction in patients breathing via a tracheal tube. The mechanism of this effect is not yet clear. Thus it can be seen that there are several possible reasons why we found smaller reductions in chest wall volume after induction of anaesthesia than would be expected from the results of other studies measuring FRC.

We found a reduction in rib cage dimensions on induction of anaesthesia, consistent with other studies [2–4, 6, 10], although earlier work failed to demonstrate this [5, 7]. The likely cause is a reduction in tonic activity in the inspiratory muscles of the rib cage. The presence of tonic activity in the scalenes, sternocleidomastoid and, to a lesser extent, in the intercostals has been demonstrated [31]; induction of anaesthesia with thiopentone abolished this. However, a study using implanted electrodes failed to demonstrate tonic activity in the parasternal intercostals [2], but the parasternal intercostals may not be representative of rib cage postural muscles [32].

We found no overall change in abdominal volumes on induction of anaesthesia, indicating that displacement of the diaphragm does not make an important contribution to the reduction in FRC. However, measurements of abdominal dimensions do not necessarily reflect changes in diaphragmatic position or length [33]. Other workers [2, 3, 34, 35] who have made direct estimates of diaphragm movements on induction of anaesthesia using x-ray and ultrasound imaging have also reported inconsistent results, and concluded that changes in length or position of the diaphragm do not contribute significantly to the reduction in FRC on induction of anaesthesia.

We found no significant differences between the eltanolone, propofol and thiopentone groups. This is at a variance with the observations of Grounds and co-workers [11] who, using similar methods, found a reduction in chest wall volume using propofol for induction of anaesthesia, but found an unexplained increase with thiopentone. However, our findings agree with those of a study reporting changes in end-expiratory lung volume after induction [28], where no significant difference was found between the effects of propofol and thiopentone. It is also interesting to note that inhalation induction of anaesthesia with halothane was associated with a reduction in FRC of a broadly similar magnitude [2] to that which we found with i.v. agents.

In summary we have found that induction of anaesthesia with three different i.v. agents produced a small decrease in chest wall volume. This was caused mostly by a reduction in rib cage volume; the changes in diaphragmatic length or position were unimportant. The time course of this decrease suggests a loss of tonic inspiratory activity, and this decrease in rib cage volume contributes to the reduction in FRC seen on induction of anaesthesia.

Acknowledgements

Dr H. J. Spens was supported by a grant from Pharmacia Ltd. The software used for data acquisition was purchased with a grant from the Association of Anaesthetists of Great Britain and Ireland.

References

1. Rehder K, Southorn PA. Influence of anesthesia on the thorax. In: Roussos C, Macklem PT, eds. *The Thorax: Lung Biology in Health and Disease, vol. 29.* New York: Marcel Dekker, 1985; 923–938.
2. Warner DO, Warner MA, Ritman EL. Human chest wall function while awake and during halothane anesthesia. I. Quiet breathing. *Anesthesiology* 1995; **82**: 6–19.
3. Krayer S, Rehder K, Beck KC, Cameron PD, Didier EP, Hoffman EA. Quantification of thoracic volumes by three-dimensional imaging. *Journal of Applied Physiology* 1987; **62**: 591–598.
4. Hedenstierna G, Strandberg A, Brismar B, Lundquist H, Svensson L, Tokics L. Functional residual capacity, thoracoabdominal dimensions, and central blood volume during general anesthesia with muscle paralysis and mechanical ventilation. *Anesthesiology* 1985; **62**: 247–254.
5. Hedenstierna G, Löfström B, Lundh R. Thoracic gas volume and chest–abdomen dimensions during anesthesia and muscle paralysis. *Anesthesiology* 1981; **55**: 499–506.
6. Jones JG, Faithfull D, Jordan C, Minty B. Rib cage movement during halothane anaesthesia in man. *British Journal of Anaesthesia* 1979; **51**: 399–407.
7. Vellody VPS, Nassery M, Balasaraswathi K, Goldberg NB, Sharp JT. Compliances of human rib cage and diaphragm–abdomen pathways in relaxed versus paralyzed states. *American Review of Respiratory Disease* 1978; **118**: 479–491.
8. Smith JC, Mead J. Three degree of freedom description of movement of the human chest wall. *Journal of Applied Physiology* 1986; **60**: 928–934.
9. Konno K, Mead J. Measurement of the separate volume changes of rib cage and abdomen during breathing. *Journal of Applied Physiology* 1967; **22**: 407–422.
10. Morton CPJ, Drummond GB. Change in chest wall dimensions on induction of anaesthesia: a reappraisal. *British Journal of Anaesthesia* 1994; **73**: 135–139.
11. Grounds RM, Maxwell DL, Taylor MB, Aber V, Royston D. Acute ventilatory changes during i.v. induction of anaesthesia with thiopentone or propofol in man. Studies using inductance plethysmography. *British Journal of Anaesthesia* 1987; **59**: 1098–1102.
12. Van Hemelrijck J, Muller P, Van Aken H, White PF. Relative potency of eltanolone, propofol, and thiopental for induction of anaesthesia. *Anesthesiology* 1994; **80**: 36–41.
13. Grounds RM, Moore M, Morgan M. The relative potencies of thiopentone and propofol. *European Journal of Anaesthesiology* 1986; **3**: 11–17.
14. Stagg D, Goldman M, Newsom Davis J. Computer-aided measurement of breath volume and time components using magnetometers. *Journal of Applied Physiology* 1978; **44**: 623–633.
15. Chadha TS, Watson H, Birch S, Jenouri GA, Schneider AW, Cohn MA, Sackner MA. Validation of respiratory inductive plethysmography using different calibration procedures. *American Review of Respiratory Disease* 1982; **125**: 644–649.
16. Stradling JR, Chadwick GA, Quirk C, Phillips T. Respiratory inductance plethysmography: calibration techniques, their validation and the effects of posture. *Bulletin Européen Physiopathologie et Respiratoire* 1985; **21**: 317–324.
17. Zimmerman PV, Connellan SJ, Middleton HC, Tabona MV, Goldman MD, Pride N. Postural changes in rib cage and abdominal volume–motion coefficients and their effect on the calibration of a respiratory inductance plethysmograph. *American Review of Respiratory Disease* 1983; **127**: 209–214.
18. Bellia V, Romano S, Sanci S, Bonsignore G. Limitations of applicability of current calibration procedures for respiratory inductive plethysmography. *Bulletin Européen Physiopathologie et Respiratoire* 1984; **20**: 341–346.
19. Werchowski JL, Sanders MH, Costantino JP, Sciurba FC, Rogers RM. Inductance plethysmograph measurement of CPAP-induced changes in end-expiratory lung volume. *Journal of Applied Physiology* 1990; **68**: 1732–1738.
20. Sackner MA, Watson H, Belsito AS, Feinerman D, Suarez M, Gonzalez G, Bizousky F, Krieger B. Calibration of respiratory inductive plethysmograph during natural breathing. *Journal of Applied Physiology* 1989; **66**: 410–420.
21. Hickey RF, Visick WD, Fairley HB, Fourcade HE. Effects of halothane anesthesia on functional residual capacity and alveolar–arterial oxygen tension difference. *Anesthesiology* 1973; **38**: 20–24.
22. Hewlett AM, Hulands GH, Nunn JF, Heath JR. Functional residual capacity during anaesthesia. 2: Spontaneous respiration. *British Journal of Anaesthesia* 1974; **46**: 486–494.
23. Don HF, Wahba M, Cuadrado L, Kelkar K. The effects of anesthesia and 100 per cent oxygen on the functional residual capacity of the lungs. *Anesthesiology* 1970; **32**: 521–529.
24. Westbrook PR, Stubbs SE, Sessler AD, Rehder K, Hyatt RE. Effects of anesthesia and muscle paralysis on respiratory mechanics in normal man. *Journal of Applied Physiology* 1973; **34**: 81–86.
25. Kimball WR, Kelly KB, Mead J. Thoracoabdominal blood volume change and its effect on lung and chest wall volumes. *Journal of Applied Physiology* 1986; **61**: 953–959.
26. Logan MR, Brown DT, Newton I, Drummond GB. Stereophotogrammetric analysis of changes in body volume associated with the induction of anaesthesia. *British Journal of Anaesthesia* 1987; **59**: 288–294.
27. Baker AB, McGinn A, Joyce C. Effect on lung volumes of oxygen concentration when breathing is restricted. *British Journal of Anaesthesia* 1993; **70**: 259–266.
28. Rutherford JS, Logan MR, Drummond GB. Changes in end-expiratory lung volume on induction of anaesthesia with thiopentone or propofol. *British Journal of Anaesthesia* 1994; **73**: 579–582.
29. Bergman NA. Reduction in resting end-expiratory position of the respiratory system with induction of anesthesia and neuromuscular paralysis. *Anesthesiology* 1982; **57**: 14–17.
30. Bickler PE, Dueck R, Prutow RJ. Effects of barbiturate anesthesia on functional residual capacity and ribcage/diaphragm contributions to ventilation. *Anesthesiology* 1987; **66**: 147–152.
31. Drummond GB. Reduction of tonic ribcage muscle activity by anesthesia with thiopental. *Anesthesiology* 1987; **67**: 695–700.
32. de Troyer A, Kelly S, Macklem PT, Zin WA. Mechanics of the intercostal space and actions of external and internal intercostal muscles. *Journal of Clinical Investigation* 1985; **75**: 850–857.
33. Mead J, Loring SH. Analysis of volume displacement and length changes of the diaphragm during breathing. *Journal of Applied Physiology* 1982; **53**: 750–755.
34. Krayer S, Rehder K, Vettermann J, Didier EP, Ritman EL. Position and motion of the human diaphragm during anesthesia–paralysis. *Anesthesiology* 1989; **70**: 891–898.
35. Drummond GB, Allan PL, Logan MR. Changes in diaphragmatic position in association with the induction of anaesthesia. *British Journal of Anaesthesia* 1986; **58**: 1246–1251.

British Journal of Anaesthesia 1996; **76**: 374–381

Slow ventilatory dynamics after isocapnic hypoxia and voluntary hyperventilation in humans: effects of isoflurane

A. DAHAN, J. VAN KLEEF, M. VAN DEN ELSEN, R. VALK AND A. BERKENBOSCH

Summary

Short-term potentiation (STP) of breathing refers to respiratory activity that persists at termination of a primary stimulus and is not related just to the dynamics of chemoreceptors. In humans, STP is activated by brief episodes of hypoxia and voluntary hyperventilation (VHV). STP exerts a stabilizing influence on breathing pattern. To investigate the effects of a subanaesthetic concentration of isoflurane on STP, we studied recovery from mild and moderate hypoxic hyperpnoea and VHV. Experiments were performed in eight healthy volunteers. If necessary, subjects were aroused to maintain a state of wakefulness. In the hypoxic studies, a control study involved 1 min of isocapnic hypoxia (end-tidal $P\text{O}_2$ ($P\text{E}'_{\text{O}_2}$ 6.1) kPa) followed by sudden transition to normoxia. In the isoflurane studies, 1 min of mild hypoxia (Iso-1 study: $P\text{E}'_{\text{O}_2}$ 6.2 kPa) and 1 min of moderate hypoxia (Iso-2 study: $P\text{E}'_{\text{O}_2}$ 5.7 kPa) were followed by sudden transition to normoxia during inhalation of 0.1 minimum alveolar concentration (MAC) of isoflurane. $P\text{E}'_{\text{CO}_2}$ was maintained at 5.9 kPa. In the VHV study, ventilatory recovery from 1 min of normoxic VHV was monitored before and during inhalation of 0.1 MAC of isoflurane. Subjects performed multiple transitions in each study. In the hypoxic studies, peak ventilation after 1 min of hypoxic stimulation did not differ between treatments. The averaged responses reached normoxic baseline after 56.3 (SEM 10.7) s in the control study ($n = 47$ transitions), 18.0 (3.3) s in the Iso-1 study ($n = 41$; $P < 0.05$ *vs* control) and 15.3 (2.4) s in the Iso-2 study ($n = 23$; $P < 0.05$ *vs* control). In the VHV studies, $\dot{V}\text{E}$ at termination of VHV was not different from baseline after 36 s in the control study. An immediate reduction to less than baseline ventilation, lasting 24 s, was present in the isoflurane study. We believe that shortening of the time required to reach baseline in the hypoxic studies, and hypoventilation at cessation of VHV in the isoflurane studies, are related to the inability to activate STP of breathing via an effect of isoflurane on respiratory neurones in the brain stem. Increasing the stimulus intensity during isoflurane inhalation (Iso-2 study) did not (re)-activate STP. (*Br. J. Anaesth.* 1996; **76**: 374–381)

Key words

Anaesthetics volatile, isoflurane. Ventilation, hypoxic response. Ventilation, hyperventilation. Hypoxia.

At termination of a respiratory stimulus, ventilatory activity (minute ventilation or phrenic nerve activity) that persists for seconds to minutes, not related only to the dynamics of peripheral or central chemoreceptors, is termed short-term potentiation (STP) of breathing (synonyms include ventilatory afterdischarge, central neuronal dynamics or respiratory memory) [1–3]. Among the various manoeuvres that make STP apparent are: termination of electrical stimulation of the carotid sinus nerve [4–6]; sudden cessation of brief episodes of hypoxia [3, 7–9]; and termination of voluntary hyperventilation (VHV) [10–14]. These manoeuvres yield a two-component change in minute ventilation ($\dot{V}\text{E}$) or phrenic nerve activity: an initial rapid decrease followed by a slower one. This slow decrease or decay is considered the manifestation of the STP of breathing. Studies in awake humans in which isocapnic hypoxia or isocapnic voluntary hyperventilation is induced to activate STP, demonstrated a time constant of the slow ventilatory decay of about 30 s [8, 10, 13] (and of about 4 s for the initial decrease in $\dot{V}\text{E}$) [8, 15]. STP is thought to originate within the pontomedullary brain stem involving neural networks that cause reverberating activity on stimulation [1].

A slow decay in $\dot{V}\text{E}$ or phrenic nerve activity at termination of hypoxia, VHV or carotid sinus stimulation may not always be present or its magnitude may be too small to be detected. This is because of mechanisms that override or counterinfluence the manifestation of STP or the inability to activate STP. Examples of the former are hypocapnia and sustained hypoxia (> 3 min). Both cause the absence or reduction of the amplitude of the slow ventilatory decay of STP but not its inactivation [4, 8, 16]. Previously, we have tested the effects of low concentrations of halothane on STP activation in humans [15]. The sudden termination of brief episodes of hypoxia caused the return of $\dot{V}\text{E}$ to baseline in 60 s in the control study and in 12 s in the halothane study. We related this finding to inactivation of STP of breathing through a direct effect of halothane on the pontomedullary brain stem. However, suggestions have been made that the ability to activate STP is related to stimulus intensity [3]. The ventilatory increase in the halothane study

ALBERT DAHAN, MD, PHD, JACK VAN KLEEF, MD, PHD, MAARTEN VAN DEN ELSEN, MD, RENÉ VALK, MD (Department of Anaesthesiology); AAD BERKENBOSCH, PHD (Department of Physiology); Leiden University Hospital, PO Box 9600, 1200 RC Leiden, The Netherlands. Accepted for publication: October 28, 1995.

Correspondence to A.D.

was less than 50% of control and may have been too small to exceed the threshold for activation of STP.

In the present study we have determined the pattern of breathing after 60 s of isocapnic hypoxic hyperpnoea and VHV in healthy volunteers before and during inhalation of low-dose isoflurane. Our main aims were: to investigate the influence of isoflurane on STP activation; to compare the influences of isoflurane on STP activation via stimulation of the peripheral chemoreflex pathway (hypoxic studies) and a suprapontine pathway (VHV studies); and to examine the effect of stimulus intensity on STP activation during inhalation of isoflurane. To do this, we determined ventilatory recovery from mild (end-tidal oxygen partial pressure ($P\mathrm{E}'_{\mathrm{O}_2}$ 6.2 kPa) and moderate hypoxic ($P\mathrm{E}'_{\mathrm{O}_2}$ 5.7 kPa) hyperpnoea. In order to prevent a reduction in the ventilatory response to hypoxia by isoflurane, we actively aroused the subjects during the studies. This procedure counter-influences the depressant effect of subanaesthetic isoflurane on the ventilatory response to acute isocapnic hypoxia [17].

Subjects and methods

We studied 10 healthy subjects (four females), aged 27–37 yr. The study was approved by the Leiden University Committee on Medical Ethics and informed consent was obtained. Subjects were asked to refrain from stimulants and depressants for at least 12 h before the experimental sessions. Before the study, on a separate day, all subjects performed a test study to determine the magnitude of their hypoxic responses. In that study four to five stepwise isocapnic decreases in $P\mathrm{E}'_{\mathrm{O}_2}$ from 14.5 to 6.2 kPa were applied. Hypoxia was maintained for 3 min. Subjects were excluded from further participation when their mean hypoxic response was 0.2 litre $\mathrm{min}^{-1}\,\%^{-1}$ or less.

During the study subjects were in a semi-recumbent position. An oronasal mask (Vital Signs, USA) was fitted before the study started. Airway gas flow was measured with a pneumotachograph connected to a differential pressure transducer (Hewlett-Packard, model 270, USA) and integrated electronically to yield a volume signal. This signal was calibrated with a motor-driven piston pump (stroke volume 1000 ml, at a frequency of 20 strokes min^{-1}). Corrections were made for the changes in gas viscosity as a result of changes in oxygen concentration of the inhaled gas mixture. The pneumotachograph was connected to a T-piece. One arm of the T-piece received a gas mixture with a flow of 50 litre min^{-1} from a gas mixing system, consisting of four mass flow controllers (Bronkhorst High Tec, F201–F203, The Netherlands) with which the flow of oxygen, carbon dioxide, nitrogen and isoflurane in nitrogen could be set individually at a desired level. Part of the nitrogen (5 litre min^{-1}) passed through an isoflurane vaporizer (Vapor 19.3, Dräger, Germany). During the control studies the vaporizer was kept in the "off" position. Flows were calibrated with flow resistance standards (Godart, The Netherlands). The instrumental deadspace was 250 ml. A Digital Equipment Corporation Programmable Digital Processor 11/23 microcomputer (IO, USA) provided control signals to the mass flow controllers, so that the composition of the inspiratory gas mixture could be adjusted to force the end-tidal carbon dioxide partial pressure ($P\mathrm{E}'_{\mathrm{CO}_2}$) and $P\mathrm{E}'_{\mathrm{O}_2}$ to follow a specific pattern in time.

The oxygen and carbon dioxide concentrations of the inspired and expired gases were measured with a gas monitor (Datex Multicap, Finland) by paramagnetic and infra-red analysis, respectively. The gas monitor was calibrated with gas mixtures of known concentrations. The isoflurane concentration was measured at the mouth with a Datex Ultima monitor (Finland). This monitor was calibrated with a gas mixture of isoflurane in nitrogen of known concentration. A pulse oximeter (Datex Satellite Plus, Finland) continuously monitored arterial oxygen saturation via a finger probe, $\dot{V}\mathrm{E}$, tidal volume ($V\mathrm{T}$), respiratory frequency (f), inspiratory time ($T\mathrm{I}$), expiratory time ($T\mathrm{E}$), $P\mathrm{E}'_{\mathrm{CO}_2}$, $P\mathrm{E}'_{\mathrm{O}_2}$ and arterial oxygen haemoglobin saturation from pulse oximetry were calculated and stored on a breath-to-breath basis.

HYPOXIC STUDIES

We used a computer controlled "dynamic end-tidal forcing system" to force the end-tidal gas concentrations to follow a prescribed pattern in time, independent of the ventilatory response [18]. The study was performed at a mild hypercapnic level with a $P\mathrm{E}'_{\mathrm{CO}_2}$ value of approximately 0.2–0.3 kPa above individual resting values. The reasons for this increase were two-fold: to perform control and isoflurane studies at similar $P\mathrm{E}'_{\mathrm{CO}_2}$ levels and to allow the end-tidal forcing system to adequately control $P\mathrm{E}'_{\mathrm{CO}_2}$ by manipulation of inspired carbon dioxide concentrations.

Initially, hypoxia was induced without isoflurane inhalation (control study). $P\mathrm{E}'_{\mathrm{O}_2}$ was lowered within three to four breaths from 14.5 to 6.1 kPa and maintained at this hypoxic level for 60 s. Thereafter $P\mathrm{E}'_{\mathrm{O}_2}$ was increased rapidly to baseline levels and maintained constant for a subsequent 120 s. Each subject performed 5–6 transitions out of hypoxia. During isoflurane inhalation each subject performed 4–6 transitions out of hypoxia ($P\mathrm{E}'_{\mathrm{O}_2}$ 6.2 kPa, Iso-1 study) and 2–3 transitions out of a deeper level of hypoxia ($P\mathrm{E}'_{\mathrm{O}_2}$ 5.7 kPa, Iso-2 study). Between transitions there was a 10-min interlude.

VOLUNTARY HYPERVENTILATION

Subjects were asked to voluntarily hyperventilate and were coached to increase their ventilation to about 60 litre min^{-1}. Respiratory frequency and tidal volume were set by the subjects. VHV was ended after 60 s at the command of one of the investigators. Subsequently, $\dot{V}\mathrm{E}$ was followed for 120 s after termination of VHV. Each subject was studied at least twice, with and without isoflurane inhalation. $P\mathrm{E}'_{\mathrm{CO}_2}$ was targeted at baseline level.

The hypoxic and VHV studies were performed on one morning session. Control studies always preceded the isoflurane studies.

The end-tidal isoflurane fraction was adjusted within 5 min to 0.125% (0.1 minimum alveolar concentrations (MAC) in the age group 25–40 yr [19]). This was done using an "overpressure" technique. Thereafter, a 20-min period preceded the isoflurane studies. The 20-min period represented 5 time constants for isoflurane brain uptake and equilibrium [20]. Throughout the studies, the end-tidal fraction was kept constant at the target level (0.125%) by manipulation of the vaporizer.

During the control and isoflurane (hypoxic and VHV) studies, the subjects listened to music. They were watched continuously by one of the investigators and instructed to keep their eyes open. If they closed their eyes we called the name of the subject and encouraged them to keep their eyes open. Data were discarded when the subject was unable to keep the eyes open.

DATA ANALYSIS: HYPOXIC STUDIES

For each transition, baseline $\dot{V}\text{E}$ was assessed by averaging over a 1-min time period before induction of hypoxia. Peak $\dot{V}\text{E}$ was determined by averaging the last two hypoxic $\dot{V}\text{E}$ breaths. The difference between peak $\dot{V}\text{E}$ and baseline $\dot{V}\text{E}$ was defined $\Delta\dot{V}\text{E}$. A two-way analysis of variance was performed on baseline $\dot{V}\text{E}$, peak $\dot{V}\text{E}$ and $\Delta\dot{V}\text{E}$. Differences between the three treatments (control, Iso-1 and Iso-2) were tested with the Student–Newman–Keuls test. Probability levels less than 0.05 were taken as significant.

To obtain information on the period of time that ventilation remained greater than baseline $\dot{V}\text{E}$, when normoxia followed hypoxia, we performed an ensemble average on the $\dot{V}\text{E}$ data of the transitions of individual subjects and on all acquired transitions. One ensemble average was performed for each of the three studies (control, Iso-1, Iso-2). The averages were calculated with linear interpolation at 3.0-s time intervals between breaths of the individual trials. By indexing on the time of the last hypoxic breath (i.e. $t = 0$), the first "non-hypoxic" data point was set at time $t = 3.0$ s. We plotted the ensemble average $\dot{V}\text{E}$ data points (± 2 SEM), which constitutes an approximately 95% confidence interval. We defined ventilation to be non-significantly different from baseline $\dot{V}\text{E}$ when the magnitude of baseline $\dot{V}\text{E}$ was within the range of the ensemble average $\dot{V}\text{E} - 2$ SEM of the first two consecutive breaths. The time at which this occurred was set at the first non-significantly different data point and defined as ΔT. An undershoot was defined as ensemble average $\dot{V}\text{E}$ data $+ 2$ SEM less than baseline $\dot{V}\text{E}$. When an undershoot occurred, the time of the first mean $\dot{V}\text{E}$ data point $- 2$ SEM which included the value of baseline $\dot{V}\text{E}$ was defined ΔT (see also fig. 1 of reference [8]). Analysis of variance was performed on ΔT obtained from the ensemble averages of individual subjects. Similar procedures were performed for $V\text{T}$, $T\text{I}$ and $T\text{E}$.

DATA ANALYSIS: VOLUNTARY HYPERVENTILATION

$\dot{V}\text{E}$ during VHV was determined by averaging the last 4 breaths of hyperventilation just before the command to end VHV. An ensemble average of all control and isoflurane transitions was performed similar to those of the hypoxic studies (see above). The data were indexed on the time of the last breath of VHV (i.e. the last breath before the command to terminate VHV).

All values are mean (SEM) unless otherwise stated.

Results

TEST STUDY

Two subjects had ventilatory responses smaller than 0.2 litre $\text{min}^{-1}\,\%^{-1}$. They were excluded from further participation. The ventilatory response of the remainder (three females, five males) ranged from 0.35 to 1.0 litre $\text{min}^{-1}\,\%^{-1}$.

HYPOXIC STUDIES

A total of 111 transitions were performed in eight subjects: 47 in the control study, 41 in the Iso-1 study and 23 in the Iso-2 study. Control of $P\text{E}'_{\text{O}_2}$ and $P\text{E}'_{\text{CO}_2}$ is shown in tables 1 and 2. The expiratory fractions of isoflurane were 0.126 (0.003)% and 0.127 (0.005)% in the Iso-1 and Iso-2 studies, respectively. All subjects were able to maintain their eyes open throughout the control and isoflurane studies.

During 1 min of hypoxic stimulation, $\dot{V}\text{E}$ increased from 15.7 (1.0) litre min^{-1} (baseline) to 25.1 (2.4) litre min^{-1} (peak hypoxia) in the control study

Table 1 Control of end-tidal $P\text{O}_2$ ($P\text{E}'_{\text{O}_2}$) for the first 30 s after transition out of hypoxia for the hypoxic studies. Control, $n = 47$; Iso-1, $n = 41$, 0.1 MAC of isoflurane; Iso-2, $n = 23$, 0.1 MAC of isoflurane. Hypoxia or time 0 is the last data point before the increase in inspired oxygen. Each data point is the ensemble average of all obtained runs. Values are mean (SEM). $^*P < 0.05$ *vs* baseline

Data point (time, s)	$P\text{E}'_{\text{O}_2}$ (kPa)		
	Control	Iso-1	Iso-2
Hypoxia (0)	6.1 (0.06)*	6.2 (0.1)*	5.7 (0.2)*
1 (3)	6.7 (0.2)*	6.7 (0.3)*	7.5 (0.4)*
2 (6)	8.6 (0.4)*	8.9 (0.4)*	11.7 (0.5)*
3 (9)	11.8 (0.4)*	12.1 (0.3)*	14.6 (0.4)
4 (12)	14.3 (0.4)	14.7 (0.3)	16.1 (0.3)
5 (15)	15.6 (0.3)	15.9 (0.2)	16.4 (0.3)
6 (18)	16.2 (0.2)	16.0 (0.2)	16.2 (0.3)
7 (21)	16.6 (0.2)	16.0 (0.2)	15.9 (0.3)
8 (24)	16.6 (0.2)	15.7 (0.2)	15.6 (0.3)
9 (27)	16.4 (0.2)	15.6 (0.2)	15.5 (0.2)
10 (30)	16.3 (0.2)	15.6 (0.2)	15.4 (0.2)

Table 2 Control of end-tidal $P\text{CO}_2$ ($P\text{E}'_{\text{CO}_2}$) for the hypoxic studies. Time segment -60 to -30 s = first 30 s of hypoxia, segment -30 to 0 = last 30 s of hypoxia, segments 0–30, 30–60, 60–90 and 90–120 s = first, second, third and fourth 30-s periods of normoxia, respectively. Values are mean (SEM)

Time segment (s)	$P\text{E}'_{\text{CO}_2}$ (kPa)		
	Control	Iso-1	Iso-2
−60 to −30	5.9 (0.02)	6.0 (0.02)	5.9 (0.03)
−30–0	5.9 (0.01)	5.9 (0.01)	5.8 (0.02)
0–30	5.9 (0.02)	5.9 (0.02)	5.9 (0.03)
30–60	5.9 (0.01)	5.9 (0.01)	5.9 (0.02)
60–90	5.9 (0.01)	5.9 (0.01)	5.8 (0.02)
90–120	5.9 (0.01)	5.9 (0.01)	5.8 (0.03)

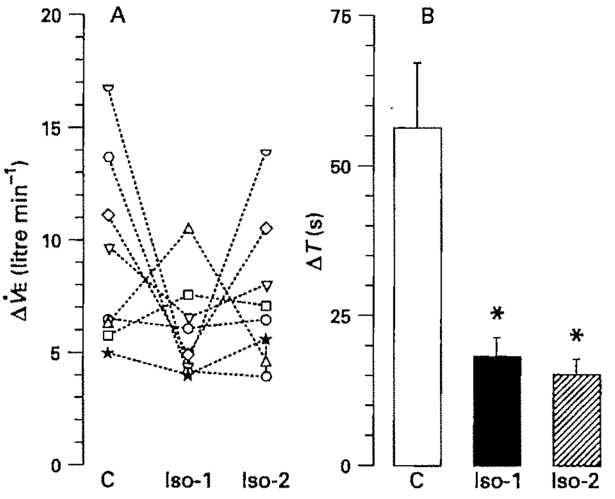


Figure 1 A: Mean ventilatory responses to 1 min of isocapnic hypoxia of individual subjects. B: Time required for $\dot{V}_E$ to return to baseline at termination of isocapnic hypoxia (ΔT). C = control study, $P_{E'_{O_2}}$ 6.1 kPa; Iso-1 = hypoxic response during inhalation of 0.1 MAC of isoflurane, $P_{E'_{O_2}}$ 6.2 kPa; Iso-2 = hypoxic response during inhalation of 0.1 MAC of isoflurane, $P_{E'_{O_2}}$ 5.7 kPa. Values are mean, SEM $^*P < 0.01$ *vs* control.

($\Delta\dot{V}_E$ 9.3 (1.5) litre min^{-1}), from 15.4 (0.6) to 21.5 (0.8) litre min^{-1} in the Iso-1 study ($\Delta\dot{V}_E$ 6.0 (0.8) litre min^{-1}) and from 15.5 (0.8) to 22.9 (1.8) litre min^{-1} in the Iso-2 study ($\Delta\dot{V}_E$ 7.5 (1.2) litre min^{-1}). The values of $\Delta\dot{V}_E$ for individual subjects is shown in figure 1A. Baseline $\dot{V}_E$, $\dot{V}_E$ at peak hypoxia and $\Delta\dot{V}_E$ did not differ significantly between the three studies.

After termination of hypoxia, the time required for $\dot{V}_E$ to reach baseline (ΔT) was 56.3 (10.7) s in the control study, 18.0 (3.3) s in the Iso-1 study ($P < 0.05$ *vs* control) and 15.3 (2.4) s in the Iso-2 study ($P < 0.05$ *vs* control) (fig. 1B). The ensemble averages of recovery from hypoxia of all obtained transitions are shown in figure 2 for the three studies. It is clear that an undershoot occurred in the Iso-1 (from $t = 21$ to 45 s) and Iso-2 (from $t = 18$ to 45 s) studies (see fig. 1).

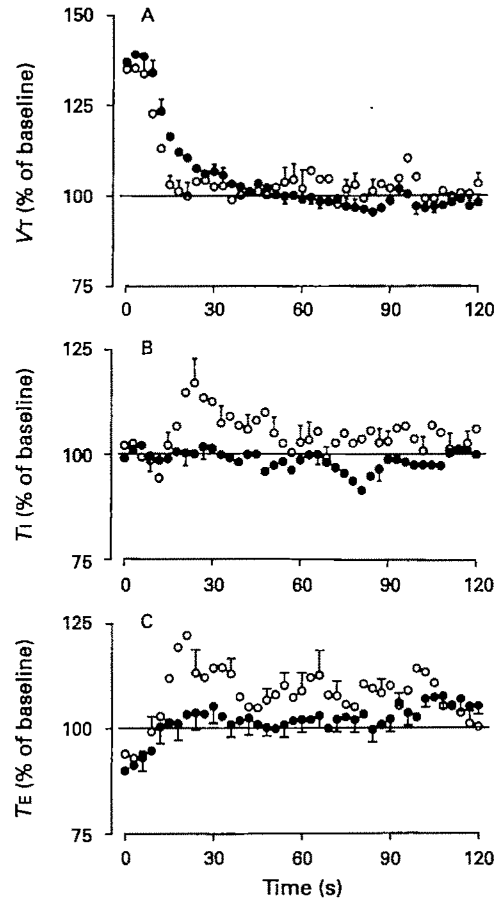


Figure 3 Ensemble averages of tidal volume (V_T) (A), inspiratory time (T_I) (B) and expiratory time (T_E) (C) of all transitions from hypoxia to normoxia (● = control; ○ = Iso-1). (See legend of fig. 2 for averaging procedure followed.)

In figure 3 we plotted the ensemble averages of the ventilatory components V_T, T_I and T_E of the control (closed circles) and Iso-1 (open circles) studies as a percentage of baseline values. In both studies the ventilatory increase at 1 min of hypoxia was caused by an increase in V_T and shortening of T_E. In the control study at cessation of hypoxia, V_T decreased

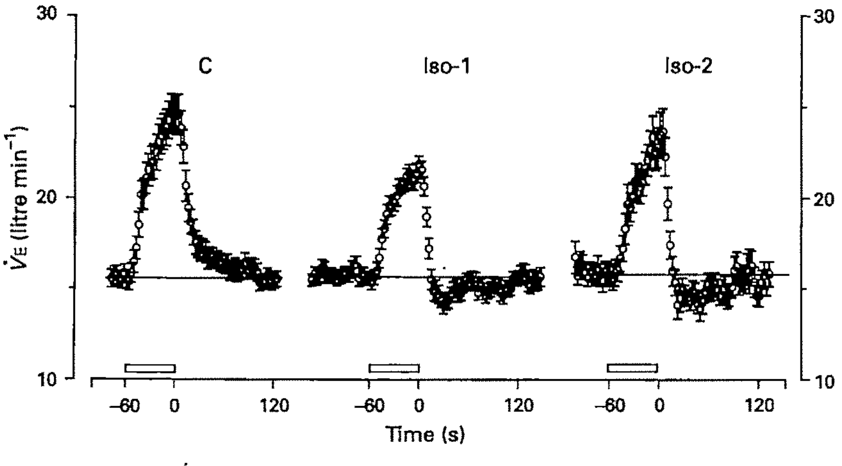


Figure 2 Ensemble averages of $\dot{V}_E$ data of all acquired transitions into and out of 1 min of isocapnic hypoxia. The averages (±2 SEM) were performed with linear interpolation at 3.0-s intervals between breaths of individual trials. Time $t = 0$ is the time of the last hypoxic breath. The first "non-hypoxic breath" is at $t = 3.0$ s. Horizontal line = baseline ventilation; bar = 1-min hypoxic period. C = Control study, $P_{E'_{O_2}}$ 6.1 kPa, $n = 47$; Iso-1 = hypoxic response during inhalation of isoflurane, $P_{E'_{O_2}}$ 6.2 kPa, $n = 41$; Iso-2 = hypoxic response during inhalation of isoflurane, $P_{E'_{O_2}}$ 5.7 kPa, $n = 23$.

Table 3 Control of end-tidal $P\mathrm{CO}_2$ ($P\mathrm{E}'_{\mathrm{CO}_2}$) for the voluntary hyperventilation (VHV) studies. VHV occurred from $t = -60$ s to $t = 0$ s. Baseline values were obtained from t -90 s to $t = -60$ s. Recovery: $t > 0$ s. Values are means (SEM). $^*P < 0.05$ *vs* baseline

Time segment (s)	$P\mathrm{E}'_{\mathrm{CO}_2}$ (kPa)	
	Control	Isoflurane
−90 to −60	5.8 (0.06)	5.8 (0.1)
−60 to −30	5.2 (0.07)*	5.5 (0.05)*
−30–0	5.6 (0.05)*	5.7 (0.02)*
0–30	6.0 (0.05)*	6.1 (0.06)*
30–60	6.0 (0.06)*	6.0 (0.06)*
60–90	5.9 (0.05)*	5.9 (0.07)*
90–120	5.8 (0.06)	5.8 (0.06)

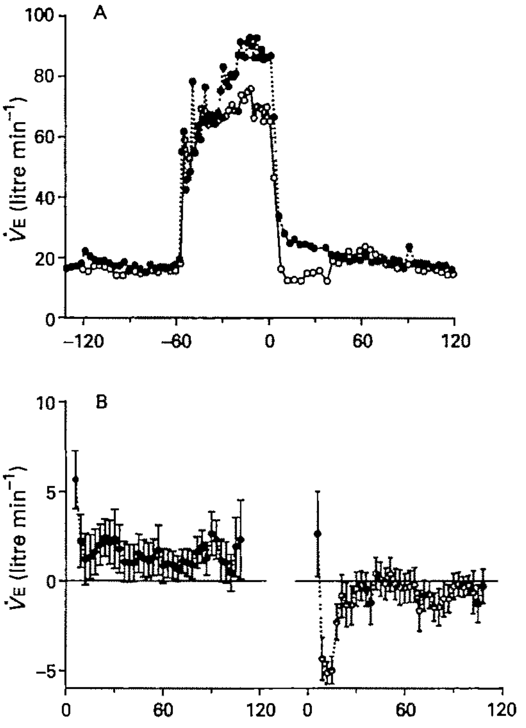


Figure 4 A: Effect of 0.1 MAC of isoflurane on ventilatory recovery from 1 min of voluntary hyperventilation. One control (●) and one isoflurane (○) experiment from a single subject are plotted. The slow decaying afterdischarge is seen in the control but not in the isoflurane experiment. Each dot is one breath. B: Ensemble averages of ventilatory recovery from voluntary hyperventilation (see legend of fig. 2 for the procedure followed). $\dot{V}\mathrm{E} = 0$ litre min^{-1} is baseline ventilation. First data point shown at $t = 6$ s. Data points are mean ± 2 SEM for the control ($n = 15$) (●) and isoflurane ($n = 15$) (○) studies.

slowly to baseline levels during the initial 51 s of normoxia. A small increase in $T\mathrm{E}$ from 90% to 100% of baseline occurred from $t = 0$ to 12 s of normoxia. The faster decay in $\dot{V}\mathrm{E}$ after hypoxia in the Iso-1 study and the undershoot below baseline was caused by changes in $V\mathrm{T}$, $T\mathrm{E}$ and $T\mathrm{I}$. Tidal volume reached baseline at $t = 18$ s, $T\mathrm{E}$ increased to ~ 125% of baseline at $t = 21$ s, and $T\mathrm{I}$ peaked to ~ 120% of baseline at $t = 27$ s of normoxia. The increases in $T\mathrm{E}$ and $T\mathrm{I}$ were followed by a slow decline towards baseline. The increase in $T\mathrm{I}$ was not immediate on cessation of hypoxia but started at $t = 15$ s of normoxia. The patterns observed in the Iso-2 study were similar to those observed in the Iso-1 study.

VOLUNTARY HYPERVENTILATION

All subjects were able to maintain their eyes open during both control and isoflurane studies. One subject failed to hyperventilate > 30 litre min^{-1} during inhalation of isoflurane. Her data were discarded from further analysis. Fifteen VHV studies during air breathing and 15 during inhalation of 0.1 MAC of isoflurane were obtained in seven subjects. Ventilation during VHV was similar in the control and isoflurane studies (control 66 (3.2) litre min^{-1} *vs* isoflurane 64 (2.5) litre min^{-1}). In contrast with the hypoxic studies, control of $P\mathrm{E}'_{\mathrm{CO}_2}$ was poor (table 3). In both studies, during VHV, $P\mathrm{E}'_{\mathrm{CO}_2}$ was consistently less than baseline values and during recovery from VHV consistently above baseline.

In figure 4A we have plotted a control and an isoflurane VHV study of one subject. In the control study, $\dot{V}\mathrm{E}$ showed an initial fast decrease followed by a slow decay. Recovery from VHV during inhalation of isoflurane displayed a fast decrease to baseline. The ensemble average of recovery from VHV is plotted in figure 4B. $\dot{V}\mathrm{E}$ remained greater than baseline for 36 s in the control study. At $t > 45$ s, $\dot{V}\mathrm{E}$ was greater than baseline for various periods. In the isoflurane study, $\dot{V}\mathrm{E}$ showed an immediate decrease to 5 litre min^{-1} below baseline followed by a slow increase (duration of undershoot 24 s).

Discussion

There was a tendency for the hypoxic ventilatory response of the Iso-1 study to decrease compared with control but this was not significant. In a previous study we observed that isoflurane at a MAC of 0.1 reduced the ventilatory response to 4 min of isocapnic hypoxia ($P\mathrm{E}'_{\mathrm{O}_2}$ 5.9 kPa) by about 50% in a similar group of subjects [21]. In retrospect, we determined the ventilatory response to 1 min of hypoxia, in a similar manner to the procedure followed in the present study, and observed a 50% reduction in the hypoxic response during isoflurane inhalation. We relate the absence of an inhibitory effect of isoflurane on the hypoxic response to additional behavioural drives that were introduced by active arousal of the subjects [17]. The introduction of additional drives such that the magnitude of the hypoxic responses between the control and isoflurane studies was not different was intentional. A reduction in hypoxic hyperpnoea by isoflurane could have resulted in a ventilatory stimulus insufficient to activate STP [3].

In the control study, ventilatory recovery from mild hypoxia ($P\mathrm{E}'_{\mathrm{O}_2}$ 6.2 kPa) showed an initial rapid decrease followed by a slow decay (ΔT ~ 56 s). In contrast, recovery from mild hypoxia during inhalation of 0.1 MAC of isoflurane showed a rapid decrease in $\dot{V}\mathrm{E}$ to just below baseline (ΔT ~ 18 s). A similar recovery pattern was observed at termination of a deeper level of hypoxia ($P\mathrm{E}'_{\mathrm{O}_2}$ 5.8 kPa) during isoflurane inhalation (ΔT ~ 15 s) (see also fig. 2). To characterize the dynamics of the ventilatory response out of hypoxia, we analysed the average responses using a simple model with two exponentials and common time delay [8, 15]. In the control study, two decaying components could be identified with time constants of 6.9 s and 126.0 s. In the isoflurane studies only one decaying component was identified with time constants of 4.2 s and 4.0 s for the Iso-1 and Iso-2 studies, respectively.

The factors that determine ventilatory recovery from brief episodes of isocapnic hypoxia are: the arterial $P\mathrm{O_2}$ waveform at the site of the peripheral chemoreceptors; the dynamics of the peripheral chemoreceptors; and activation of STP of breathing. An effect of isoflurane on one or more of these factors may be responsible for the reduction in ΔT.

At termination of hypoxia, the time at which the peripheral chemoreceptors detect normoxia depends on the $P\mathrm{E'_{O_2}}$ waveform (table 1), the (small) end-tidal to arterial $P\mathrm{O_2}$ gradient and the 5–6-s transport time from the lungs to the carotid bodies [22–24]. The loss of the hypoxic drive further depends on the fast dynamics of the peripheral chemoreceptors (time to peak discharge of the carotid sinus nerve after a sudden change in arterial $P\mathrm{O_2}$ is 1–5 s [25, 26]). We estimated that return to pre-hypoxic levels of the afferent input from the carotid bodies to the respiratory centres in the brain stem occurred between $t \sim 15$ s (time of the last hypoxic breath plus transport delay time) and $t \sim 18$ s (time of the first non-hypoxic breath plus transport delay time) of normoxia in the control study. We assumed that isoflurane, at the concentrations we have used, did not influence any of the above-mentioned factors and estimated the loss of hypoxic drive in the Iso-1 and Iso-2 studies between $t \sim 15$ and ~ 18 s and between $t \sim 12$ and ~ 15 s of normoxia, respectively.

The slow decay present during normoxic recovery from hypoxia in the control study is the manifestation of STP of breathing. Its time constant was larger than those observed in previous studies [8, 15]. The main difference between these studies is the higher $P\mathrm{E'_{CO_2}}$ background in the present study. Data from Fregosi in awake humans suggest that more intense stimuli (for example hypoxia plus exercise or hypoxia plus hypercapnia) result in longer periods of potentiation compared with less intense stimuli (hypoxia at rest, hypoxia plus normocapnia) [3].

In the Iso-1 study the absence of the slow decay of $\dot{V}\mathrm{E}$ during recovery from hypoxic hyperpnoea caused the reduction in ΔT (fig. 2). Furthermore, despite the more intense hypoxic stimulus, and the tendency for the ventilatory response to increase, a slow decay did not appear in the recovery pattern of the Iso-2 study. The time for $\dot{V}\mathrm{E}$ to return to baseline in the isoflurane studies was equal to the loss of hypoxic drive. These findings indicate that in both isoflurane studies, arterial $P\mathrm{O_2}$ and the dynamics of the peripheral chemoreceptors determined ventilatory decay and that central neuronal dynamics were not activated. As the ventilatory responses did not differ between treatments, the inability to activate STP was not related to the intensity of the hypoxic stimulus or to the magnitude of response, but to an effect of isoflurane. This is probably a specific effect on those respiratory neurones within the pontomedullary brain stem responsible for STP activation. However, an indirect effect of isoflurane, for example via an altered CNS arousal state, cannot be excluded (see below). Isoflurane and halothane [15] behave identically with respect to STP inactivation. It is noteworthy that in animal studies, STP of breathing is activated by various stimuli despite anaesthesia [1, 5]. It is possible that apart from the species difference this may be because of differences in stimulus intensities and techniques to activate STP.

In the control study we observed that the slow decay in $\dot{V}\mathrm{E}$ was predominantly because of potentiation of $V\mathrm{T}$ with no contribution from inspiratory and expiratory times (fig. 3). Similar observations have been made by Georgopoulos and colleagues [9]. During isoflurane inhalation, potentiation of $V\mathrm{T}$ was abolished. Furthermore, an increase in both $T\mathrm{E}$ and $T\mathrm{I}$ caused the decrease in $\dot{V}\mathrm{E}$ to less than baseline $\dot{V}\mathrm{E}$ (fig. 3). These changes waned slowly: at times > 120 s, $T\mathrm{I}$ and $T\mathrm{E}$ did not differ from baseline. It is not clear if the prolongation of the inspiratory and expiratory times and inactivation of STP (i.e. no potentiation of $V\mathrm{T}$) occurred at distinct anatomical sites within the CNS. For now we consider these phenomena together: they cause rapid changes in $\dot{V}\mathrm{E}$ and immediate hypoventilation at cessation of isocapnic hypoxic hyperpnoea.

We were unable to maintain strict control of $P\mathrm{E'_{CO_2}}$ in the VHV studies. This was partly because of the relatively low inspiratory gas flow that was insufficient for the minute volumes of the subjects during VHV. As a consequence, a mixture of air, expired gas via the expiratory limb and fresh gas via the inspiratory limb of the breathing system was inhaled with an inspired carbon dioxide concentration lower than the target concentration. The gain and time constant of the computer driven $P\mathrm{E'_{CO_2}}$ control were intentionally not altered to avoid $P\mathrm{E'_{CO_2}}$ oscillations and high inspired carbon dioxide concentrations. As $P\mathrm{E'_{CO_2}}$ waveforms were similar in the control and isoflurane studies, we consider comparison of the $\dot{V}\mathrm{E}$ recovery patterns from VHV between the two studies a valid procedure to demonstrate a possible effect of isoflurane on STP.

Despite the decrease in $P\mathrm{E'_{CO_2}}$ during VHV, $\dot{V}\mathrm{E}$ remained greater than baseline during the first 36 s of recovery in the control study (table 3, fig. 4B). This is attributed to activation of STP of breathing. Our data are consistent with the observation of others [10–14]. We relate the elevated $\dot{V}\mathrm{E}$ at > 45 s to the increase in $P\mathrm{E'_{CO_2}}$ during the first 90 s of recovery from VHV. In the isoflurane study, recovery from VHV displayed immediate hypoventilation during the first 24 s of normoxia. The absence of STP activation because of the central effects of isoflurane now yielded a ventilatory pattern dominantly controlled by the chemical stimuli to the chemoreceptors (i.e. hypoventilation because of hypocapnia). In healthy volunteers Wilkins, Reed and Aitkenhead noticed hypoventilation and arterial desaturation after 2 min of poikilocapnic VHV during inhalation of 50% nitrous oxide in oxygen but not while inhaling 50% nitrogen in oxygen [27]. Northwood and co-workers tested the effects of 75% nitrous oxide in oxygen on the recovery pattern from poikilocapnic ($P\text{E}'_{CO_2} \sim 3$ kPa) VHV in six normal subjects [12]. They observed apnoea and arterial desaturation in all subjects when told to relax after VHV (duration of apnoea 80 s; lowest saturation 75 %). We relate these observations to inactivation of STP of breathing by nitrous oxide, a property it shares with isoflurane. The results of our VHV studies are in agreement with those of our hypoxic studies. This indicates that slow central neuronal dynamics activated via a peripheral chemoreflex pathway and via a suprapontine pathway are equally sensitive to the effects of low-dose isoflurane.

We were unable to exclude explicitly the fact that the subjects cycled between arousal states ("sleep"–wakefulness) during recovery from hyperpnoea. It is therefore possible that our observations were influenced by an altered CNS arousal state. Fink and colleagues described the observation of post-hyperventilation apnoea in a subject who fell asleep at the end of VHV and resumed breathing on waking [28]. As alteration of the CNS arousal state is an inherent property of isoflurane, we feel that a distinction between the action on the ponto-medullary brain stem of the agent itself or its indirect action via an alterated arousal state is somewhat artificial. Furthermore, we do not believe that such a distinction would make our conclusions less valid.

STP exerts a stabilizing influence on $\dot{V}\text{E}$ [29]. For example, the absence of STP is observed in patients with congestive heart failure and nocturnal Cheyne–Stokes breathing [30]. In a previous study we showed that termination of 20 min of isocapnic hypoxia by normoxia results in a rapid decrease in $\dot{V}\text{E}$ to pre-hypoxic baseline. However, the identical procedure performed during inhalation of subanaesthetic halothane resulted in an undershoot 30% below normoxic baseline and in some subjects in the occurrence of central apnoea and arterial haemoglobin desaturation to < 80% [31]. We relate these ventilatory instabilities to inactivation of STP (see also [8]). Bearing in mind the fact that our studies have been performed in healthy volunteers, the findings from our current study and those of others [12, 15, 27] that inhalation anaesthetics, directly or indirectly, cause inability to activate STP may have important clinical implications. After surgery, inhalation anaesthetics persist for several hours in the body [32] and STP inactivation may, in part, be related to the frequent occurrence of hypoxic episodes after operation [15]. Furthermore, anaesthetics are often used for sedation or analgesia in a variety of clinical procedures. Hyperventilation and hypocapnia (for example because of pain or fear) may be followed by hypoventilation and arterial desaturation on administration of anaesthetics [12]. We suggest therefore that the arterial oxygenation of patients who breathe spontaneously and are or were exposed to inhalation anaesthetics should be monitored continuously using pulse oximetry.

References

1. Eldridge FL, Kiley JP, Paydarfar. Dynamics of medullary hydrogen ion and respiratory neurons to square-wave change of arterial carbon dioxide in cats. *Journal of Physiology (London)* 1987; **385**: 627–642.
2. Eldridge FL, Millhorn DE. Oscillation, gating, and memory in the respiratory control system. In: Fishman AP, Cheniack NS, Widdicombe JG, Geiger SR, eds. *Handbook of Physiology, section 3, The Respiratory System, vol. 2, Control of Breathing, part 1*. Bethesda, MD, USA: American Physiological Society, 1986; 93–114.
3. Fregosi RF. Short-term potentiation of breathing in humans. *Journal of Applied Physiology* 1991; **71**: 892–899.
4. Eldridge FL. Subthreshold central neuronal respiratory activity and afterdischarge. *Respiration Physiology* 1990; **39**: 327–343.
5. Vis A, Folgering HTh. Phrenic nerve afterdischarge after electrical stimulation of the carotid sinus nerve in cats. *Respiration Physiology* 1981; **45**: 217–227.
6. Wagner PG, Eldridge FL. Development of short-term potentiation of respiration. *Respiration Physiology* 1991; **83**: 129–140.
7. Badr MS, Skatrud JB, Dempsey JA. Determinants of poststimulus potentiation in humans during NREM sleep. *Journal of Applied Physiology* 1992; **73**: 1958–1971.
8. Dahan A, Berkenbosch A, DeGoede J, van den Elsen M, Olievier I, van Kleef J. Influence of hypoxic duration and post-hypoxic inspired O_2 concentration on short term potentiation of breathing in humans. *Journal of Physiology (London)* 1995; **488**: 803–813.
9. Georgopoulos D, Bshouty Z, Younes M, Anthonisen NR. Hypoxic exposure and activation of afterdischarge mechanisms in conscious humans. *Journal of Applied Physiology* 1990; **69**: 1159–1164.
10. Folgering H, Durlinger M. Time course of post-hyperventilation breathing in humans depends on $P\text{CO}_2$. *Journal of Applied Physiology* 1983; **54**: 809–813.
11. Meah MS, Gardner WN. Post-hyperventilation apnoea in conscious humans. *Journal of Physiology (London)* 1994; **477**: 527–538.
12. Northwood D, Sapsford DJ, Jones JG, Griffiths D, Wilkins C. Nitrous oxide sedation causes post-hyperventilation apnoea. *British Journal of Anaesthesia* 1991; **67**: 7–12.
13. Swanson GD, Ward DS, Bellville JW. Posthyperventilation isocapnic hyperpnoea. *Journal of Applied Physiology* 1976; **40**: 592–596.
14. Tawadrous FD, Eldridge LF. Posthyperventilation breathing patterns after active hyperventilation in man. *Journal of Applied Physiology* 1974; **37**: 353–356.
15. Dahan A, van den Elsen MJLJ, Berkenbosch A, DeGoede J, Olievier ICW, van Kleef JW. Halothane affects ventilatory afterdischarge in man. *British Journal of Anaesthesia* 1995; **74**: 544–548.
16. Engwall MJA, Smith CA, Dempsey JA, Bisgard GE. Ventilatory afterdischarge and central respiratory drive interactions in the awake goat. *Journal of Applied Physiology* 1994; **76**: 416–423.
17. van den Elsen MJLJ, Dahan A, DeGoede J, Berkenbosch A, van Kleef JW, Olievier ICW. Does subanesthetic isoflurane affect the ventilatory response to acute isocapnic hypoxia in healthy volunteers? *Anesthesiology* 1994; **81**: 860–867.
18. Dahan A, DeGoede J, Berkenbosch A, Olievier ICW. The influence of oxygen on the ventilatory response to carbon dioxide in man. *Journal of Physiology (London)* 1990; **428**: 485–499.
19. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI II, Miller RD, DeJong RH, Elashoff RM. Minimum alveolar concentration (MAC) of isoflurane with and without nitrous oxide in patients of various ages. *Anesthesiology* 1975; **42**: 197–200.
20. Eger EI II. *Anesthetic Uptake and Action*. Baltimore: Williams & Wilkins, 1974.
21. van den Elsen MJLJ, Dahan A, DeGoede J, Berkenbosch A, van Kleef J. Influences of subanesthetic isoflurane on ventilatory control in humans. *Anesthesiology* 1995; **83**: 478–490.
22. Nunn JF. *Nunn's Applied Respiratory Physiology*. Oxford: Butterworth-Heinemann Ltd, 1993.
23. Clement ID, Robbins PA. Latency of the ventilatory chemoreflex response to hypoxia in humans. *Respiration Physiology* 1993; **92**: 277–287.
24. Dahan A. *The Ventilatory Response to Carbon Dioxide and Oxygen in Man: Methods and Implications*. PhD thesis. Leiden: University of Leiden, 1990.
25. Black AMS, McCloskey DI, Torrance RW. The response of

the carotid body chemoreceptors in the cat to sudden changes in hypercapnic and hypoxic stimuli. *Respiration Physiology* 1971; **13**: 36–49.

26. Ponte J, Purves MJ. Frequency response of carotid body chemoreceptors in the cat to changes of Pa_{CO_2}, Pa_{O_2}, and pH. *Journal of Applied Physiology* 1974; **37**: 635–647.
27. Wilkins CJ, Reed PN, Aitkenhead AR. Hypoxaemia after inhalation of 50% nitrous oxide and oxygen. *British Journal of Anaesthesia* 1989; **63**: 346–347.
28. Fink BR, Hanks EC, Ngai SH, Pappar EM. Central regulation of respiration during anesthesia and wakefulness. *Annals of the New York Academy of Sciences* 1963; **109**: 892–900.
29. Younes M. The physiological basis of central apnea and periodic breathing. *Current Pulmonology* 1989; **10**: 265–326.
30. Ahmed M, Serrette C, Kryger MH, Anthonisen NR. Ventilatory instability in patients with congestive heart failure and nocturnal Cheyne–Stokes breathing. *Sleep* 1994; **17**: 527–534.
31. Dahan A, van den Elsen MJLJ, Berkenbosch A, DeGoede J, Olievier ICW, Burm AGL, van Kleef JW. Influence of a subanesthetic concentration of halothane on the ventilatory response to step changes into and out of sustained isocapnic hypoxia in healthy volunteers. *Anesthesiology* 1994; **81**: 850–859.
32. Carpenter RL, Eger EI II, Johnson BH, Undakat JD, Sheiner LB. Pharmacokinetics of inhaled anesthetics in humans. Measurements after the simultaneous administration of enflurane, halothane, isoflurane, methoxyflurane, and nitrous oxide. *Anesthesia and Analgesia* 1986; **65**: 575–582.

British Journal of Anaesthesia 1996; 76: 382–388

Comparison of the pharmacodynamics and pharmacokinetics of an infusion of *cis*-atracurium (51W89) or atracurium in critically ill patients undergoing mechanical ventilation in an intensive therapy unit

A. H. BOYD, N. B. EASTWOOD, C. J. R. PARKER AND J. M. HUNTER

Summary

We have studied 12 critically ill, sedated patients who required a neuromuscular blocking drug to assist mechanical ventilation in an intensive care unit. Patients were randomized to receive an infusion of *cis*-atracurium 0.18 mg kg^{-1} h^{-1} (group 1, $n = 6$) or atracurium 0.6 mg kg^{-1} h^{-1} (group 2, $n = 6$) preceded, if necessary, by a bolus dose of $2 \times ED_{95}$ of the same drug (*cis*-atracurium 0.1 mg kg^{-1} or atracurium 0.5 mg kg^{-1}). Neuromuscular block was monitored using an accelerograph and the infusion rate adjusted regularly so that it was possible to detect the first response to train-of-four (TOF) stimulation of the ulnar nerve at the wrist. Blood samples were obtained for estimation of plasma *cis*-atracurium and laudanosine concentrations (group 1) or the three groups of atracurium isomers and laudanosine (group 2). There was no apparent haemodynamic or allergic response to either drug. The mean infusion time in group 1 was 37.6 h and in group 2, 27.5 h. On termination of the infusion, the time for the TOF ratio to reach 0.7 was similar in the two groups (group 1 = 60 min; group 2 = 62 min). The mean infusion rate of *cis*-atracurium was 0.19 mg kg^{-1} h^{-1} and of atracurium 0.47 mg kg^{-1} h^{-1} (expressed as mg of bis-cation): *cis*-atracurium was 2.5 times more potent than atracurium. Using the NONMEM program, a single compartment pharmacokinetic model was fitted to the plasma concentrations of *cis*-atracurium and the *cis-cis, cis-trans* and *trans-trans* isomers of atracurium. The mean population pharmacokinetic values for *cis*-atracurium were: volume of distribution (V) = 21 900 (SEM 416) ml; clearance (Cl) = 549 (79) ml min^{-1}; half-life ($T_{\frac{1}{2}}$) = 27.6 (3.6) min; and for the three groups of atracurium isomers were: *cis-cis*, $V = 15100$ (720) ml, $Cl = 449$ (42) ml min^{-1}, $T_{\frac{1}{2}} = 23.4$ (1.2) min; *cis-trans*, $V = 18000$ (667) ml, $Cl = 1070$ (43) ml min^{-1}, $T_{\frac{1}{2}} = 11.7$ (0.1); *trans-trans*, $V = 13100$ (1280) ml, $Cl = 1560$ (55) ml min^{-1}, $T_{\frac{1}{2}} = 5.8$ (0.4) min. Plasma laudanosine concentrations were lower in the *cis*-atracurium (peak value 1.3 μg ml^{-1}) than in the atracurium (maximum 4.4 μg ml^{-1}) group. (*Br. J. Anaesth.* 1996; **76**: 382–388)

Key words

Neuromuscular block, atracurium. Neuromuscular block, 51W89. Pharmacokinetics, atracurium. Pharmacodynamics. Intensive care. Pharmacokinetics, stereoisomers.

In the management of critically ill patients requiring mechanical ventilation in an intensive care unit, it may occasionally be necessary to administer a neuromuscular blocking drug together with sedative and analgesic agents. Indications for the use of neuromuscular blocking agents in such circumstances include: poor lung compliance, as in patients with adult respiratory distress syndrome; inability to synchronize the patient's own respiratory pattern with intermittent positive pressure ventilation (IPPV); raised intracranial pressure; status epilepticus; and to facilitate radiological imaging or inter-hospital patient transfer [1].

Atracurium, given by constant infusion, has proved useful in the management of the critically ill. It breaks down spontaneously in plasma (Hofmann elimination) and undergoes ester hydrolysis [2]. Thus its clearance is partially independent of renal and hepatic function, making it suitable for use in patients with multiple organ failure (MOF) [3]. Laudanosine, a metabolite of Hofmann degradation, is excreted partly by the kidney [4] and also by the liver [5]. Electroencephalographic changes in cats have been reported at plasma concentrations of > 4.4 μg ml^{-1} and convulsions in rats and dogs at a concentration of 17 μg ml^{-1} [6–8]. In pharmacokinetic studies of critically ill patients receiving atracurium by constant infusion without neuromuscular monitoring, plasma concentrations of laudanosine of up to 5 μg ml^{-1} have been detected [9, 10]. Although this concentration is higher than after a single bolus dose of atracurium 0.5–0.6 mg kg^{-1}, when plasma laudanosine concentrations peak at approximately 0.2–0.3 μg ml^{-1} [11, 12] there is as yet no evidence to suggest that laudanosine concentrations reported in patients with MOF are epileptogenic.

Atracurium is a mixture of 10 geometric isomers

A. H. BOYD, MB, CHB, FRCA, N. B. EASTWOOD, BSC, MB, BS, FRCA, C. J. R. PARKER, MA, MD, FRCA, J. M. HUNTER, MB, CHB, PHD, FRCA, University Department of Anaesthesia, Royal Liverpool University Hospital, Prescot Street, Liverpool L69 3BX. Accepted for publication: October 17, 1995.

each with different pharmacological characteristics [13]. There are three groups of these isomers: *cis-cis*, *cis-trans* and *trans-trans* atracurium. The 1R *cis*-1′R *cis* isomer, designated 51W89 and given the generic name, *cis*-atracurium, has been shown in humans to be approximately three times more potent than atracurium [14], to release less histamine [15] and, in animals, to have a higher affinity for the postsynaptic nicotinic receptor [16]. As a smaller mass of drug is required to produce the same degree of neuromuscular block, it would be expected that degradation of *cis*-atracurium might produce lower plasma laudanosine concentrations than those detected after atracurium.

This study was therefore designed to compare *cis*-atracurium with atracurium, given by constant infusion, in critically ill patients requiring neuromuscular block to facilitate mechanical ventilation. The aim was to assess dose requirements and any possible side effects of *cis*-atracurium. Plasma concentrations of *cis*-atracurium and the three groups of isomers of atracurium were measured and an attempt was made to compare the pharmacokinetics of *cis*-atracurium with the individual isomer groups of atracurium. The plasma laudanosine concentrations produced by the two drugs were also compared.

Patients and methods

The study was approved by the Hospital Ethics Committee. A clinical trial exemption certificate for the use of *cis*-atracurium was issued by the Committee on Safety of Medicines. Informed consent was obtained from the next of kin of all patients. Twelve patients, aged > 18 yr, were investigated consecutively, after a predetermined randomized sequence; six were allocated to receive *cis*-atracurium (group 1) and six to receive atracurium (group 2). Patients were considered suitable for entry into this study only when their medical management required the use of a neuromuscular blocking agent. Exclusion criteria included: pregnancy; known sensitivity to atracurium; personal or family history of malignant hyperthermia; clinically significant neuromuscular disease; major thermal injury; recent administration of a neuromuscular blocking agent for more than 24 h in the presence of renal failure; failure to demonstrate partial recovery of the train-of-four count after a previously administered neuromuscular blocking agent; prior administration of atracurium of more than 3 mg kg^{-1} within the previous 8 h; or administration of an atracurium infusion within the previous 4 days.

All patients admitted to the intensive therapy unit (ITU) were treated as indicated clinically, with sedative and analgesic agents given in accordance with the sedation policy of the ITU. If the patient had already received a neuromuscular blocking agent and did not have any of the exclusion criteria listed above, evidence of recovery from neuromuscular block was sought, using an accelerograph, before inclusion in the study. Thus a previously administered neuromuscular blocking agent might have been detectable in the plasma on entry into the study.

The physical characteristics, medical history and diagnosis of each patient were recorded (table 1), and also all medications administered in the 12-h period before and during administration of the neuromuscular blocking agent (table 2). A physical examination was performed and baseline recordings of vital signs such as arterial pressure, heart rate and temperature. Blood samples were obtained for estimation of haemoglobin, MCV, platelet count, white cell count, and serum concentrations of sodium, potassium, bicarbonate, creatinine, total bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin and glucose. Illness severity scores (Apache II) [17] were recorded for the 24-h period immediately after commencement of the study. Urine was analysed for protein and blood.

Neuromuscular monitoring was quantified using an accelerograph (TOF-Guard, Biometer, Denmark). The skin over the ulnar nerve at the wrist was cleansed and gently abraided. Paediatric electrocardiographic electrodes were then applied to allow stimulation of the ulnar nerve at the wrist, using the train-of-four (TOF) twitch technique. The transducer was attached to the thumb to measure acceleration in response to contraction of the adductor pollicis muscle. The accelerograph records both the TOF count (T1, T2, T3, T4) and the TOF ratio (T4:T1), expressed as a percentage. Baseline measurements were determined before administration of the neuromuscular blocking agent.

Depending on the clinical situation, a bolus of the neuromuscular blocking agent followed by a constant infusion of the same drug was commenced or, if the patient had already received such a drug, the infusion was started without a bolus dose.

Those patients receiving *cis*-atracurium (group 1) were given a bolus dose of $2 \times ED_{95}$ (0.1 mg kg^{-1}), over 5–10 s, followed immediately by an initial infusion of 0.18 mg kg^{-1} h^{-1}; alternatively, a constant infusion was started at the same rate. Patients receiving atracurium (group 2) were given a bolus of $2 \times ED_{95}$ (0.5 mg kg^{-1}) or an initial infusion of 0.6 mg kg^{-1} h^{-1}, or both. The infusion of *cis*-atracurium or atracurium was subsequently adjusted to maintain the TOF count at 1 response only (T1). As few adjustments as possible to the infusion rates were made, and any changes were small. A record of the TOF count was noted whenever the infusion rate was changed, and at least once every 8 h if no alteration in the infusion rate had occurred during that period. The TOF count was also documented just before discontinuing the infusion and every 5 min thereafter until the TOF ratio was > 0.7.

A blood sample (5 ml) was obtained from each patient before administration of the drug. Further samples were obtained 15 min and 1 h after the initial bolus dose of either *cis*-atracurium or atracurium, or after commencement of the infusion (if a bolus dose had not been given). Blood samples were then obtained 15 min and 1 h after any alteration in the infusion rate and approximately every 8 h, if there had been no alteration in the infusion rate. Samples were also collected immediately before termination of the drug, at 2, 5, 10 and 20 min after

Table 1 Clinical details of the 12 patients studied. IPPV = Intermittent positive pressure ventilation; ARDS = adult respiratory distress syndrome; RTA = road traffic accident; MOF = multiple organ failure. ▼ = Patients with renal failure (see figs 1, 2). Apache scores are for the 24 h after commencing the infusion. P = Propofol, M = morphine, A = alfentanil, Mi = midazolam, C = clonazepam, D = diamorphine

Patient No.	Age (yr)	Weight (kg)	Sex (M/F)	Apache II score	Diagnosis	Sedation and analgesia	Outcome
Group 1: *cis*-atracurium							
1	71	65	F	9	Repair of ruptured abdominal aortic aneurysm, re-exploration for bleeding, ARDS, pneumonia	P, M	Survived
2	38	50	F	22	Cardiorespiratory arrest, chronic alcohol abuse, MOF, renal failure ▼	P, A	Discharged to ward; readmitted 3 days later, died
3	25	75	M	8	Asthma, acute respiratory failure	P, M	Survived
4	69	75	M	10	Pneumonia, respiratory failure, septicaemia, MOF	P, M	Died in ITU 10 days after infusion
5	60	70	M	22	Myocardial infarction, cardiac arrest, hypoxic brain injury, insulin-dependent diabetes mellitus	C	Died in ITU 6 days after infusion
6	22	80	M	19	RTA, basal skull fracture, extradural haemorrhage, ruptured diaphragm, fractured jaw, fractured femur	P, M	Died in ITU 1 day after infusion
Group 2: atracurium							
7	56	77	M	28	Streptococcal septicaemia, MOF, renal failure ▼	P, D, Mi	Died in ITU with infusion in progress
8	50	80	F	3	IPPV postoperatively after right nephrolithotomy, non-insulin-dependent diabetes mellitus	P, M	Survived
9	67	65	F	20	Thrombotic thrombocytopenia, respiratory failure, renal failure ▼, ARDS, MOF	P, D, Mi	Died in ITU 31 days after infusion
10	59	74	M	13	Myocardial infarction, cardiac arrest, hypoxic brain injury	P, D, Mi	Survived
11	61	80	M	21	Brain stem infarct, hypertension	P	Died in ITU 2 days after infusion
12	60	70	M	17	Renal artery stenosis, renal failure ▼. Admitted postoperatively after attempted revascularization of left kidney. Ischaemic bowel	P, M	Died in ITU 6 days after infusion

termination, and at 1, 3, 6, 12, 24, 36, 48, 72 and 96 h, wherever possible,

Each blood sample was placed immediately into a lithium heparin tube containing 0.02 ml of sulphuric acid 1.5 mol litre^{-1} and centrifuged. The plasma (2 ml) was decanted and acidified with 8 ml of sulphuric acid 15 mmol litre^{-1}. The acidified plasma was kept on ice and deep frozen within 30 min for subsequent analysis by solid phase extraction and high pressure liquid chromatography (HPLC) with fluorescence detection. The assay was validated using quality control samples derived from pooled human plasma. The lower limit of quantification (LOQ) was 10 ng ml^{-1} for all analytes. In group 1, the upper LOQ for *cis*-atracurium was 2140 ng ml^{-1} and for laudanosine 1410 ng ml^{-1}. In group 2 the upper LOQ values for *cis-cis*, *cis-trans* and *trans-trans* isomers of atracurium were 2800, 1580 and 250 ng ml^{-1}; the upper LOQ for laudanosine was 2000 ng ml^{-1}. The coefficient of variation for all analytes was $< 11.3\%$, except for the *trans-trans* atracurium isomers, which was 20.8%.

The non-linear mixed effects model program (NONMEM) [18] was used to fit a one-compartment model to the plasma concentrations of *cis*-atracurium from patients in group 1, and to the plasma concentration profiles of each of the atracurium isomer groups in those patients who received atracurium (group 2). The program fits a model to the data for all individuals collectively; rather than attempting to identify the pharmacokinetic variables of each individual separately, a population mean is determined. In principle, the inter-individual random variability in pharmacokinetic variables is also determined, but these results are not presented in view of the small sample size.

The models were described in terms of compartment volume and clearance. Elimination half-life was determined in additional NONMEM runs with the model described in terms of V and $T_{\frac{1}{2}}$. Attempts to fit a two-compartment model were unsatisfactory, presumably as a consequence of the sparsity of data points in the periods just after starting and finishing the infusion. In one patient who received atracurium (patient No. 7), the final three plasma concentrations were obtained soon after extensive debridement of soft tissue under general anaesthesia and within a few hours of death. Their inclusion in the data set used to fit the model was associated with large residual errors and difficulty in obtaining convergence of the routine to minimize the objective function. They were therefore omitted from the data set used to fit the model.

Results

The physical characteristics and diagnoses of the patients are shown in table 1. Patient No. 6 had received atracurium 135 mg and vecuronium 74 mg in the 24 h before admission into the study: he had

Table 2 Plasma urea and electrolyte concentrations, and liver function tests in each patient at the beginning of the study. N/A = not available

Patient No.	Na⁺ (mmol litre⁻¹)	K⁺ (mmol litre⁻¹)	HCO_3^- (mmol litre⁻¹)	Urea (mmol litre⁻¹)	Creatinine (μmol litre⁻¹)	Bilirubin (μmol litre⁻¹)	ALP (iu litre⁻¹)	ALT (iu litre⁻¹)	AST (iu litre⁻¹)	Albumin (mmol litre⁻¹)	Glucose (mmol litre⁻¹)
Reference range	135–145	3.5–5.4	20–30	2.5–7.0	50–130	2–17	35–125	< 35	< 45	36–52	3.5–5.5
Group 1: *cis*-atracurium											
1	136	4.1	30	14.7	129	57	61	21	N/A	33	7.0
2	153	3.3	26	9.5	223	32	54	68	288	34	14.5
3	140	4.0	28	3.5	77	5	99	29	32	39	7.3
4	139	3.5	30	5.9	73	59	139	20	29	36	10.5
5	134	3.5	22	13.4	148	17	140	679	317	38	19.1
6	161	2.9	23	5.8	108	N/A	N/A	N/A	N/A	N/A	6.1
Group 2: atracurium											
7	133	4.5	22	17.2	308	169	124	25	42	36	5.8
8	139	4.2	18	3.3	82	13	60	25	32	30	19.5
9	144	4.2	21	28.4	690	16	55	21	48	30	8.6
10	141	3.7	17	6.5	101	5	80	64	221	41	10.3
11	140	2.9	28	10.7	134	19	84	8	20	38	7.0
12	130	4.2	21	23.1	752	10	81	34	81	33	9.8

surgery for orthopaedic procedures and had also been transferred to another hospital for intracranial surgery during that time. Patient No. 9 had received vecuronium 10 mg, 2.5 h previously. Urea and electrolyte concentrations and liver function tests in each patient on entering the study are shown in table 2.

Medication administered to each patient concurrent with the infusion of neuromuscular blocking drug is given in table 3. All patients completed the study except for patient No. 7 who died while an infusion of atracurium was in progress. Brain stem death, after a severe head injury, was diagnosed in patient No. 6, 19.5 h after discontinuation of the infusion.

Of the six patients who received *cis*-atracurium, five were given an initial bolus dose together with an infusion. Patient No. 6, who had received atracurium and vecuronium before inclusion in the study, still had evidence of residual neuromuscular block when entered into the study (TOF count = 1). He received no initial bolus dose. The mean infusion rate for each patient, number of changes of the infusion rate, duration of each infusion and total dose given are shown in table 4. The TOF count on discontinuing the infusion and the time for the TOF ratio to reach greater than 0.7 are also given. The mean infusion rate for patients given *cis*-atracurium was 0.19 (range 0.16–0.21) mg kg^{-1} h^{-1} and the mean time for the TOF ratio to reach 0.7 was 60 (20–85) min.

Five patients were given a bolus of atracurium followed immediately by an infusion. Atracurium was initiated by infusion to patient No. 9, who had previously been given vecuronium, but she required an additional bolus 15 min later. The mean infusion rate for atracurium in group 2 was 0.47 (range 0.3–0.74) mg kg^{-1} h^{-1}. The mean duration of infusion for the atracurium group was shorter than that for the *cis*-atracurium group (27.53 *vs* 37.62 h). In patient No. 10 it was not possible to measure the time to a TOF ratio > 0.7 because of a fault with the accelerograph. The mean time to achieve a TOF ratio greater than 0.7 was 62 (41–82) min in the four other patients.

Analysis of the two batches of *cis*-atracurium used in the study showed one batch to contain 105.8 % of the stated amount (5 mg ml^{-1}) and the other to contain 110.1 %. Analysis of the atracurium used in the study indicated that it contained 109.2 % of the stated amount (10 mg ml^{-1}) and the following isomer composition: *cis-cis* 58.7 %, *cis-trans* 35.9 %, *trans-trans* 5.4 %. Pharmacokinetic variables, derived using the NONMEM program for *cis*-atracurium and each of the three groups of isomers of atracurium, are given in table 5.

The plasma concentrations of laudanosine in each of the patients during the infusion are shown in figure 1, and after discontinuing the infusion in figure 2.

As patient No. 7 died while still receiving an infusion of atracurium, there are only 11 plots in figure 2. Peak laudanosine concentrations obtained and values for area under curve of laudanosine against time are given in table 6. The peak plasma laudanosine concentration in patients given *cis*-

Table 3 Concomitant medication during period of infusion of *cis*-atracurium or atracurium

Patient no.	
Cis-atracurium	
1	Dobutamine, noradrenaline, insulin, frusemide, ranitidine, salbutamol, ciprofloxacin, ceftazidime
2	Dobutamine, noradrenaline, insulin, metronidazole, cefotaxime, ampicillin, folinic acid, salbutamol, parentrovite, ipratropium bromide, sucralfate, ranitidine, heparin
3	Aminophylline, salbutamol, ipratropium bromide, hydrocortisone
4	Dobutamine, noradrenaline, glyceryl trinitrate, methylprednisolone, ranitidine, ipratropium bromide, salbutamol, nystatin, heparin, erythromycin
5	Lignocaine, insulin, clonazepam, isosorbide, dexamethasone, ranitidine
6	Dobutamine, phenytoin, mannitol, metronidazole, cefotaxime, ranitidine, fentanyl, DDAVP
Atracurium	
7	Dobutamine, adrenaline, noradrenaline, metronidazole, benzylpenicillin, amphotericin, phenytoin, ranitidine, insulin
8	Cefotaxime, salbutamol, ranitidine, insulin, gentamicin, heparin
9	Insulin, dobutamine, enoximone, calcium gluconate, sandoglobulin, hydrocortisone, methylprednisolone, ranitidine, prostacyclin
10	Dobutamine, isosorbide, ranitidine, magnesium sulphate
11	Ranitidine, glyceryl trinitrate, sodium nitroprusside, cefotaxime, metronidazole, frusemide
12	Glyceryl trinitrate, amiodarone, salbutamol, metronidazole, co-amoxiclav, ceftazidime, erythromycin, heparin, ranitidine

Table 4 Mean infusion rate required (with starting and finishing rate), infusion duration and total dose of *cis*-atracurium or atracurium given to the 12 patients, together with the number of infusion changes and the TOF count immediately before discontinuing the infusion. The time from the end of the infusion to recovery of the TOF > 0.7 is also given (*peripheral temperature = 29.7 °C; N/A = not available as patient died). Dose of *cis*-atracurium and atracurium in mg of bis-cation

Patient No.	Mean (initial – final) infusion rate ($mg\ kg^{-1}\ h^{-1}$)	Total dose (mg) (bolus + infusion)	Infusion duration (h)	No. of infusion rate changes	TOF count before stopping infusion	Time to TOF > 0.7 (min)
Group 1: *cis*-atracurium						
1	0.2 (0.19–0.21)	612	47.59	2	0	75
2	0.18 (0.19–0.16)	376	41.27	1	4	50
3	0.19 (0.19–0.19)	568	39.2	0	4	20
4	0.18 (0.19–0.17)	558	41.13	1	2	60
5	0.19 (0.19–0.17)	323	24.3	1	0	70
6	0.19 (0.19–0.19)	493	32.22	0	0	85*
Group 2: atracurium						
7	0.71 (0.50–0.64)	1668	30.08	3	N/A	N/A
8	0.44 (0.49–0.41)	1229	34.24	1	0	50
9	0.41 (0.50–0.38)	796	29.92	1	0	75
10	0.30 (0.30–0.30)	462	19.33	0	0	—
11	0.49 (0.49–0.49)	911	22.40	0	0	41
12	0.49 (0.49–0.49)	1018	29.2	0	0	82

Table 5 Population pharmacokinetic variables as population mean (SEM), for *cis*-atracurium and the atracurium isomer groups, derived using the NONMEM program (one-compartment model)

	Group 1:	Group 2: atracurium		
	cis-atracurium	*cis-cis*	*cis-trans*	*trans-trans*
V (ml)	21900 (416)	15100 (720)	18000 (667)	13100 (1280)
Cl ($ml\ min^{-1}$)	549 (79)	449 (42)	1070 (43)	1560 (55)
$T_{\frac{1}{2}}$ (min)	27.6 (3.6)	23.4 (1.2)	11.7 (0.1)	5.8 (0.4)
Coefficient of variation of residual error (%)	41.5	30.7	40.6	46.4
No. of data points	81	64	62	50

atracurium was 1.3 $\mu g\ ml^{-1}$, whereas in patients who received atracurium it was 4.4 $\mu g\ ml^{-1}$.

No haemodynamic disturbances or allergic reactions were associated with either the bolus dose or infusion of both neuromuscular blocking agents.

Discussion

In this study, the mean infusion rates of *cis*-atracurium and atracurium required for six critically ill patients were 0.19 and 0.47 $mg\ kg^{-1}\ h^{-1}$, respectively. The mean infusion rate of *cis*-atracurium was comparable with that reported by Stone, Pollard and Harper (0.17 $mg\ kg^{-1}\ h^{-1}$) in 12 intensive care patients [19]. The atracurium infusion rates were also similar to those reported in other studies in the critically ill [10, 20]. In this study, *cis*-atracurium was therefore approximately 2.5 times more potent than atracurium (with the dose of both drugs expressed as milligrams of the bis-cation). The dose of atracurium in the commercial preparation is expressed as milligrams of the salt: for our patients,

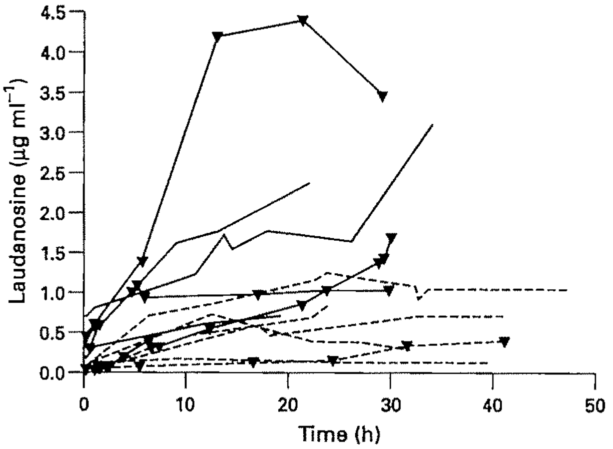


Figure 1 Plasma laudanosine concentrations *vs* time during the period of infusion of *cis*-atracurium (– – –) or atracurium (——). ▼ = Patients with renal failure.

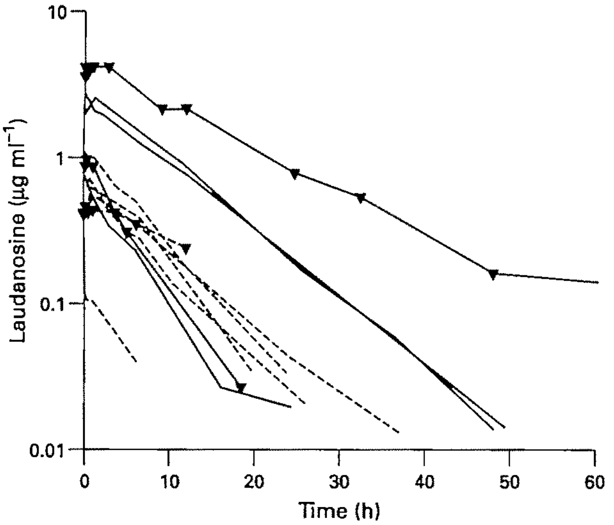


Figure 2 Log plasma laudanosine concentrations *vs* time after stopping the infusion of *cis*-atracurium (– – –) or atracurium (——). ▼ = Patients with renal failure.

Table 6 Peak plasma laudanosine concentrations and AUC for individual patients. (AUC = Area under curve for laudanosine concentration *vs* time)

Patient No.	Peak laudanosine (μg ml^{-1})	AUC (μg ml^{-1} h)
Cis-atracurium		
1	1.26	54.1
2	0.44	17.2
3	0.21	7.7
4	0.73	27.1
5	0.85	12.6
6	0.75	20.6
Atracurium		
7	1.7	20.5
8	3.13	84.1
9	1.05	34.1
10	0.78	14.8
11	2.80	61.5
12	4.40	166.3

this is equivalent in clinical use to atracurium 0.63 mg kg^{-1} h^{-1}.

An infusion of *cis*-atracurium provided adequate neuromuscular block in our patients. As with previous clinical studies of this new drug [15], no obvious adverse cardiovascular or allergic effects were noted. None was noted in the atracurium group. Allergic responses to drugs are, in fact, uncommon in critically ill patients [21]. On discontinuing the infusion, the mean time for the TOF ratio to recover to greater than 0.7 was very similar after *cis*-atracurium or atracurium (60 *vs* 62 min). The TOF count on stopping the infusion, measured using the accelerograph, varied between 0 and 4 in patients given *cis*-atracurium, but was 0 in all patients given atracurium. However, we noted that it was possible, on occasion, to see the first response to the TOF without it being detected by the accelerograph. We do not therefore believe that there were significant differences in the degree of neuromuscular block on discontinuing the infusion between the patients studied; the accelerograph is not always accurate for use in this group of patients. It was chosen because it is compact, easy to use and does not require immobilization of the patient's arm for long periods of time. The time to achieve a TOF ratio > 0.7 of 60 min after either drug compares very favourably with vecuronium, after which the time to achieve a similar degree of recovery may taken more than 35 h in patients with MOF [22]. It is interesting to note that in the vecuronium study, the possibility of metronidazole inhibiting metabolism of the drug was raised [22]. Five of the patients in this study were receiving metronidazole (table 3), but there was no evidence of such an effect. It would seem that rapid recovery can be achieved after *cis*-atracurium has been given for many hours to critically ill patients, in the same way as has been reported after the use of atracurium [3, 20].

There was no evidence for the development of tolerance to the action of each of the neuromuscular agents in the two groups. In the *cis*-atracurium group, only patient No. 1 required a slightly greater infusion rate at the end of the study than at the beginning. In the atracurium group, a similar pattern was found: only patient No. 7 had increased requirements at the end of the infusion period. Although the maximum duration of infusion was only 47.6 h in group 1 and 34.2 h in group 2, Stone, Pollard and Harper also found no evidence for increasing requirements of *cis*-atracurium with time, even after infusions of up to 135 h duration. Evidence for the development of tolerance to neuromuscular blocking agents in the critically ill is mainly anecdotal [9] although it has been demonstrated in paediatric practice and in anaesthetized dogs [23, 24].

In the pharmacokinetic analysis of plasma concentrations of *cis*-atracurium (group 1) and the three groups of atracurium isomers (group 2), it was only possible to fit a one-compartment pharmacokinetic model to the data because of the relative sparsity of data points for individual patients at the times when the infusion was changed. Clearance of *cis*-atracurium was found to be 549 ml min^{-1}, with an elimination half-life of 28 min. These values were similar to those found in a study of healthy patients and patients with chronic renal failure given a bolus dose of *cis*-atracurium 0.1 mg kg^{-1} [25]. It was reassuring to find that the clearance of *cis*-atracurium was unchanged, and possibly increased, in these six critically ill patients. Once again there is evidence of spontaneous atracurium (or its isomer) breakdown irrespective of the residing body compartment [10, 12].

It is interesting to compare the pharmacokinetics of *cis*-atracurium with those of the three *cis-cis* isomers of atracurium (group 2), where clearance was 449 ml min^{-1} and $T_{\frac{1}{2}}$ 23 min. These differences probably reflect the presence of the two other *cis-cis* isomers in atracurium. There were other differences in the derived pharmacokinetic variables for the three groups of atracurium isomers. Clearance of the *cis-trans* isomer was approximately twice that of the *cis-cis* isomer, and that of the *trans-trans* group over three times that of the *cis-cis* isomer. The values for clearance and elimination half-life of the *cis-cis* and *cis-trans* isomers in this study were comparable with those of Tsui, Graham and Torda in a study of eight ASA I and II patients who were given a single bolus dose of atracurium 0.3 or 0.5 mg kg^{-1} [26]. These workers did not determine the kinetics of the very short-acting *trans-trans* isomer. Our study is the first to examine the pharmacokinetics of the three groups of isomers of atracurium in the critically ill patient.

Plasma laudanosine concentrations were smaller after *cis*-atracurium than after atracurium. The highest measured plasma concentration of laudanosine in group 1 was 1.3 µg ml^{-1}, and in group 2 4.4 µg ml^{-1}. Laudanosine concentrations after atracurium were comparable with those reported previously in the critically ill [9, 10]. No attempt was made to fit a pharmacokinetic model to the plasma laudanosine concentrations for several reasons. After administration of *cis*-atracurium or atracurium, laudanosine is produced continually as a metabolite at various sites. Thus the total dose of laudanosine given is unknown and the time course of laudanosine production cannot be determined. The AUC was calculated, however, to give an indication of the overall formation of laudanosine; it tended to be less in the group who received *cis*-atracurium than atracurium.

Acknowledgement

We thank the Wellcome Foundation plc for providing a grant towards this study and the *cis*-atracurium and atracurium.

References

1. Coursin DB, Kelly JS, Prielipp RC. Muscle relaxants in critical care. *Current Opinion in Anesthesiology* 1993; **6**: 341–346.
2. Stenlake JB, Waigh RD, Dewar GH, Hughes R, Chapple DJ, Coker GG. Biodegradable neuromuscular blocking agents. Part 4. Atracurium besylate and related polyalkylene diesters. *European Journal of Medicinal Chemistry* 1981; **16**: 515–524.
3. Griffiths RB, Hunter JM, Jones RS. Atracurium infusions in patients with renal failure on an ITU. *Anaesthesia* 1986; **41**: 375–381.
4. Fahey MR, Rupp SM, Canfell C, Fisher DM, Miller RD, Sharma M, Castagnoli K, Hennis PJ. Effect of renal failure on laudanosine excretion in man. *British Journal of Anaesthesia* 1985; **57**: 1049–1051.
5. Lawhead RG, Matsumi M, Peters KR, Landers DF, Becker GL, Earl RA. Plasma laudanosine levels in patients given atracurium during liver transplantation. *Anesthesia and Analgesia* 1993; **76**: 569–573.
6. Ingram MD, Sclabassi RJ, Stiller RL, Cook DR, Bennett MH. Cardiovascular and electroencephalographic effects of laudanosine in nephrectomized cats. *Anesthesia and Analgesia* 1985; **64**: 232.
7. Scheepstra GL, Vree TB, Crul JF, Van de Pol F, Reekers-Ketting J. Convulsive effects and pharmacokinetics of laudanosine in the rat. *European Journal of Anaesthesiology* 1986; **3**: 371–383.
8. Chapple DJ, Miller AA, Ward JB, Wheatley PL. Cardiovascular and neurological effects of laudanosine. *British Journal of Anaesthesia* 1987; **59**: 218–225.
9. Yate PM, Flynn PJ, Arnold RW, Weatherly BC, Simmonds RJ, Dopson T. Clinical experience and plasma laudanosine concentrations during the infusion of atracurium in the intensive therapy unit. *British Journal of Anaesthesia* 1987; **59**: 211–217.
10. Parker CJR, Jones JE, Hunter JM. Disposition of infusions of atracurium and its metabolite, laudanosine, in patients in renal and respiratory failure in an ITU. *British Journal of Anaesthesia* 1988; **61**: 531–540.
11. Fahey MR, Rupp SM, Fisher DM, Miller RD, Sharma M, Canfell C, Castagnoli K, Hennis PJ. The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. *Anesthesiology* 1984; **61**: 699–702.
12. Parker CJR, Hunter JM. Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis. *British Journal of Anaesthesia* 1989; **62**: 177–183.
13. Stenlake JB, Waigh RD, Dewar GH, Dhar NC, Hughes R, Chapple DJ, Lindon JC, Ferrige AG, Cobb PH. Biodegradable neuromuscular blocking agents. Part 6—stereochemical studies on atracurium and related polyalkylene di-esters. *European Journal of Medicinal Chemistry* 1984; **19**: 441–450.
14. Belmont MR, Lien CA, Quessy S, Abou-Donia MM, Abalos A, Eppich L, Savarese JJ. The clinical neuromuscular pharmacology of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. *Anesthesiology* 1995; **82**: 1139–1145.
15. Lien CA, Belmont MR, Abalos A, Eppich L, Quessy S, Abou-Donia MM, Savarese JJ. The cardiovascular effects and histamine-releasing properties of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. *Anesthesiology* 1995; **82**: 1131–1138.
16. Wastila WB, Maehr RB. The pharmacological profile of 51W89, the R *cis*-R′*cis* isomer of atracurium in cats. *Anesthesiology* 1993; **79**: A946.
17. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Critical Care Medicine* 1985; **13**: 818–829.
18. Beal SL, Sheiner LB. *NONMEM Users' Guide*. San Francisco: University of California, 1979.
19. Stone AJ, Pollard BJ, Harper NJN. Infusion requirements of patients receiving 51W89 in the intensive care unit. *British Journal of Anaesthesia* 1994; **72**: 486–487P.
20. Wadon AJ, Dogra S, Anand S. Atracurium infusion in the intensive care unit. *British Journal of Anaesthesia* 1986; **58**: 64–67S.
21. Hunter JM. Histamine release and neuromuscular blocking drugs. *Anaesthesia* 1993; **48**: 561–563.
22. Smith CL, Hunter JM, Jones RS. Vecuronium infusions in patients with renal failure in an ITU. *Anaesthesia* 1987; **42**: 387–393.
23. Kushimo OT, Darowski MJ, Morris P, Hollis S, Meakin G. Dose requirements of atracurium in paediatric intensive care patients. *British Journal of Anaesthesia* 1991; **67**: 781–783.
24. Chapple DJ, Dodd P, MacLeod DM, Withington PS, Yate PM. Requirements for neuromuscular blocking agents during prolonged anaesthesia in the anaesthetized dog. *British Journal of Anaesthesia* 1987; **59**: 1321–1322P.
25. Eastwood NB, Boyd AH, Parker CJR, Hunter JM. Pharmacokinetics of 1R-*cis* 1′R-*cis* atracurium besylate (51W89) and plasma laudanosine concentrations in health and chronic renal failure. *British Journal of Anaesthesia* 1995; **75**: 431–435.
26. Tsui D, Graham GG, Torda TA. The pharmacokinetics of atracurium isomers in vitro and in humans. *Anesthesiology* 1987; **67**: 722–728.

British Journal of Anaesthesia 1996; 76: 389–395

Effect of isoflurane and sevoflurane on the magnitude and time course of neuromuscular block produced by vecuronium, pancuronium and atracurium†

L. E. H. VANLINTHOUT, L. H. D. J. BOOIJ, J. VAN EGMOND AND E. N. ROBERTSON

Summary

We have compared the ability of equipotent concentrations of isoflurane and sevoflurane to enhance the effect of non-depolarizing neuromuscular blocking drugs. Ninety ASA I and II patients of both sexes, aged 18–50 yr, were stratified into three blocker groups (Vec, Pan and Atr), to undergo neuromuscular block with vecuronium ($n = 30$), pancuronium ($n = 30$) or atracurium ($n = 30$), respectively. Within each group, patients were allocated randomly to one of three anaesthetic subgroups to undergo maintenance of anaesthesia with: (1) alfentanil–nitrous oxide–oxygen ($n = 10$); (2) alfentanil–nitrous oxide–oxygen–isoflurane ($n = 10$); or (3) alfentanil–nitrous oxide–oxygen–sevoflurane ($n = 10$) anaesthesia. During maintenance of anaesthesia, end-tidal concentrations of isoflurane, sevoflurane and nitrous oxide were 0.95, 1.70 and 70%, respectively. Both the evoked integrated electromyogram and mechanomyogram of the adductor pollicis brevis muscle were measured simultaneously. In the Vec and Pan groups, a total dose of 40 $\mu g\ kg^{-1}$ of vecuronium or pancuronium, respectively, was given, and in the Atr group a total dose of atracurium 100 $\mu g\ kg^{-1}$. Each blocker was given in four equal doses and administered cumulatively. We showed that 0.95% isoflurane and 1.70% sevoflurane (corresponding to 0.8 MAC of each inhalation anaesthetic, omitting the MAC contribution of nitrous oxide) augmented and prolonged the neuromuscular block produced by vecuronium, pancuronium and atracurium to a similar degree. (*Br. J. Anaesth.* 1996; **76**: 389–395)

Key words

Anaesthetics volatile, isoflurane. Anaesthetics volatile, sevoflurane. Measurement techniques, electromyography. Measurement techniques, mechanomyography. Neuromuscular block, vecuronium. Neuromuscular block, pancuronium. Neuromuscular block, atracurium.

Various inhalation anaesthetics augment neuromuscular block produced by non-depolarizing neuromuscular blocking agents to a different degree. Although sevoflurane appears to increase both intensity and duration of neuromuscular block induced by vecuronium and pancuronium [1–4], the magnitude of this effect has not been quantified in a homogeneous population. Such information is clinically relevant; for example potentiation of blocker effect during administration of sevoflurane and reversal of this potentiation on withdrawal of this short-acting inhalation agent may reduce blocker dose requirements in the peroperative period and decrease the risk of residual curarization after operation.

Previous studies comparing the effects of isoflurane and sevoflurane on vecuronium block have produced inconclusive results. These studies were unable to show any significant difference for the effects of 1.15% isoflurane and 1.70% sevoflurane (both with 70% nitrous oxide [1, 2]) or for the effects of 1.15% isoflurane and 2.05% sevoflurane (both with 66% nitrous oxide [3]) on the block produced by vecuronium. Another interaction study, comparing opioid–nitrous oxide–oxygen and opioid–nitrous oxide–oxygen–sevoflurane anaesthesia, could not demonstrate any significant influence of sevoflurane with concentrations less than 2% on the duration of vecuronium-induced block [4].

In order to clarify the inconsistencies in the literature on the interactions between sevoflurane and neuromuscular blockers, we have compared the effect of equipotent concentrations of isoflurane and sevoflurane on non-depolarizing neuromuscular block in a carefully selected, homogeneous population of young adults. In this population the minimum alveolar concentrations (MAC) of isoflurane and sevoflurane in air–oxygen were found to be 1.15% [5] and 2.05% [6], respectively. The addition of 65–70% nitrous oxide reduces the MAC of both agents to 0.50% [5] and 1.10% [7], respectively.

Patients and methods

After obtaining approval from the Institutional Review Board and written informed consent, we studied 90 healthy adult patients, aged 18–50 yr, of both sexes, ASA I or II, undergoing elective surgical

---

L. E. H. VANLINTHOUT, MD, L. H. D. J. BOOIJ, MD, PHD, FRCA, J. VAN EGMOND, PHD, E. N. ROBERTSON, MD, FRCA, Institute for Anaesthesiology, University Hospital of Nijmegen, Geert Grooteplein 10, PO Box 9101, 6500 HB Nijmegen, The Netherlands.
Accepted for publication: October 10, 1995.

Correspondence to L.E.H.V.

†Presented in part at the American Society of Anesthesiologists Annual Meeting, San Francisco, October 15–19, 1994.

procedures of an anticipated duration of $\geqslant$ 90 min under general anaesthesia. Patients were excluded if they had cardiac, pulmonary, renal, hepatic, neurological, psychiatric, muscular, inflammatory, malignant or endocrine diseases, as were pregnant women and patients with recent exposure (< 72 h) to medications known to interfere with neuromuscular transmission. Those more than 20 % overweight, according to life insurance tables [8], or those with clinical laboratory abnormalities (i.e. serum electrolyte, creatinine, BUN, SGOT, LDH, alkaline phosphatase or GGT concentrations) were also excluded.

Patients were stratified into one of three blocker groups (Vec, Pan, and Atr) consisting of 30 patients each. Within each blocker group, patients were allocated randomly to one of three anaesthetic subgroups, to undergo maintenance of anaesthesia with either: (1) alfentanil–nitrous oxide–oxygen (non-halogenated anaesthetics group (NHA)) (n = 10); (2) alfentanil–nitrous oxide–oxygen–isoflurane (isoflurane group (Iso)) (n = 10); or (3) alfentanil–nitrous oxide–oxygen–sevoflurane (sevoflurane group (Sev)) (n = 10).

After an overnight fast, patients were premedicated with diazepam 0.1 mg kg^{-1} orally, 60–90 min before induction of anaesthesia. Before this, patients were given Ringer's solution 1.5 ml kg^{-1} per hour of fasting. Alfentanil 100 μg kg^{-1} was administered as a bolus i.v. followed by a variable rate infusion of alfentanil 0.5–1.5 μg kg^{-1} min^{-1}. Three minutes after the alfentanil infusion was started, anaesthesia was induced with propofol 3.5–5 mg kg^{-1} i.v. in divided doses. The trachea was intubated without neuromuscular block. Anaesthesia was maintained with the anaesthetic technique selected during the randomization procedure. End-tidal concentrations of isoflurane, sevoflurane and nitrous oxide were targeted at 0.95 %, 1.70 % and 70 %, respectively. For the population studied, the MAC values of isoflurane and sevoflurane in air–oxygen were defined as 1.15 % [5] and 2.05 % [6], respectively. The contribution of nitrous oxide to the MAC value of the inhalation agent was calculated applying the concept of additivity of MAC fractions, where the individual MAC values of each gas (in this case nitrous oxide and sevoflurane or isoflurane) are summated to find the MAC value of the combination [9]. Equipotent concentrations of isoflurane and sevoflurane were defined as equal fractions of the MAC of either volatile anaesthetic without the MAC contribution of nitrous oxide [10].

After 40 min of stable end-tidal anaesthetic concentrations (within 5 % of the target values), an end-tidal carbon dioxide partial pressure of 4.7–5.3 kPa, stable haemodynamics with a systolic arterial pressure > 100 mm Hg and a stable baseline neuromuscular transmission recording, the blocker was administered i.v. in a cumulative manner, as described below. During the procedure both central and thenar skin temperatures were maintained between 35.5 and 36.5 °C using surface heating.

ECG monitoring of lead II was performed continuously and arterial pressure was measured intermittently by automated sphygmomanometry (Dinamap, Criticon, Tampa, USA). The arterial pressure cuff was placed on the arm opposite to the site where neuromuscular transmission was assessed. Thenar skin temperature was monitored using a thermocouple placed on the dorsum of the hand from which the response to ulnar nerve stimulation was recorded. Central temperature was measured using a rectal probe. The end-tidal concentrations of carbon dioxide, nitrous oxide, isoflurane and sevoflurane were measured continuously and displayed by a multiple gas analyser (Capnomac Ultima, Datex). This gas analyser was calibrated once every week using a calibrating gas (Quick Cal, Datex). Neuromuscular transmission was evaluated using both the evoked integrated electromyogram (IEMG) and the mechanomyogram (MMG) of the ipsilateral adductor pollicis muscle. The stimulating current, consisting of supramaximal rectangular pulses (duration 100 μs) into a train-of-four (TOF) pattern (frequency 2 Hz), was generated by the stimulating unit of the Datex Relaxograph and delivered every 20 s (0.05 Hz) to the ulnar nerve at the wrist via s.c. 27-gauge steel needle electrodes, placed 30 mm apart. The hand and forearm were immobilized in supination and abduction on a splint and the fingers were strapped in extension. The thenar electromyographic signal was detected using gelled silver–silver chloride skin electrodes. These were placed over the belly of the adductor pollicis muscle (the active recording electrode), at the distal phalanx of the second finger (the reference recording electrode) and midway between the stimulating and recording electrodes (grounding electrode). The force transducer was mounted so that the thumb was exposed to a preload of 200 *g*, measured continuously and recorded. During the study, a preload of 100–300 *g* was accepted.

For each blocker group, a cumulative dosing regimen was designed in which all patients undergoing maintenance of anaesthesia with different anaesthetic techniques were given the same amount of neuromuscular blocking agent. In the Vec and Pan groups, a total dose of 40 μg kg^{-1} of vecuronium or pancuronium, respectively, was given and in the Atr group a total dose of atracurium 100 μg kg^{-1} was given. Each blocker was injected in four equal doses and administered cumulatively. For vecuronium and pancuronium, an initial dose of 10 μg kg^{-1} and three increments of 10 μg kg^{-1} each were administered. For atracurium, an initial dose of 25 μg kg^{-1} and three increments of 25 μg kg^{-1} each were administered. Each dose of neuromuscular blocking agent was injected as an i.v. bolus over < 5 s into a rapidly running infusion.

As soon as the patient was anaesthetized, baseline evaluations of neuromuscular transmission were started and continued for 40 min before administration of the neuromuscular blocking agent. The mean of 10 first twitch (T1) responses, immediately preceding the first administration of neuromuscular blocking agent, became the control to which all subsequent T1 responses were compared. Each dose increment was given (at times $t1$, $t2$ and $t3$, respectively) only after the effect of the previous dose had reached a stable response, defined as three equal

Table 1 Patient characteristics (mean (pooled SEM or range)) in the different anaesthetic subgroups within the vecuronium, pancuronium and atracurium groups. NHA = No halogenated anaesthetic ($n = 10$), Iso = isoflurane ($n = 10$), Sev = sevoflurane ($n = 10$). % Ideal wt = body weight expressed as percentage of ideal weight for height. Within the three blocker groups, there were no significant differences between the subgroups NHA, Iso and Sev in age, weight and % ideal wt

Group	Anaesthetic technique	Age (yr)	Weight (kg)	% Ideal wt	Sex (M/F)
Vecuronium	NHA	33.2 (19–45)	67.0 (3.8)	97.0 (3.3)	4/6
($n = 30$)	Iso	30.3 (20–47)	71.3 (3.8)	98.2 (3.3)	7/3
	Sev	28.9 (19–48)	72.3 (3.8)	102.0 (3.3)	7/3
Pancuronium	NHA	32.5 (18–46)	63.2 (3.6)	99.4 (3.5)	6/4
($n = 30$)	Iso	33.1 (18–50)	67.6 (3.6)	101.8 (3.5)	4/6
	Sev	32.6 (21–45)	72.5 (3.6)	99.4 (3.5)	7/3
Atracurium	NHA	33.5 (24–47)	68.8 (3.2)	99.3 (3.6)	4/6
($n = 30$)	Iso	32.8 (21–49)	75.0 (3.2)	102.5 (3.6)	4/6
	Sev	37.1 (21–50)	73.1 (3.2)	101.5 (3.6)	5/5

(±1%) consecutive IEMG or MMG T1 responses, or when 7 min had passed with no decrease in T1 from control.

DATA ANALYSIS

Age, weight and percentage of ideal weight for height between the nine subgroups were compared using one-way analysis of variance (ANOVA). The Ryan–Einot–Gabriel–Wesch multiple range test (REGW test) [11] was applied subsequently to identify eventual sources of difference.

Within each blocker group, the time schedule in which the four doses of the neuromuscular blocking agents were administered was compared between the three anaesthetic subgroups, by comparing the times to injection of the first (*t*1), second (*t*2) and third (*t*3) increments after administration of the initial dose, using one-way ANOVA. The REGW test was applied subsequently to identify eventual sources of difference.

The individual dose–effect relationship was examined by plotting the logarithm of the dose against the logit transformation of T1 depression relative to control

$$\text{Logit(E)} = \alpha \times \log_e D - \beta$$

where $\text{Logit(E)} = \log_e(\text{E}/(\text{Emax} - \text{E}))$; E = T1 depression relative to control (%); Emax = maximal effect, that is 100%; D = dose, administered cumulatively; α = steepness coefficient; and β = intercept.

Because logit 0 and logit 1 do not exist, 0% and 100% T1 depression were considered as missing values. Lines of best fit were computed using linear least squares regression. The doses required for 50%, 90% and 95% T1 depression (ED_{50}, ED_{90} and ED_{95}, respectively) were calculated from the regression line.

The regression lines were tested to determine if they deviated from parallelism [12]. If they did not, ED_{50}, ED_{90} and ED_{95} values were compared between the subgroups. Parallelism was tested using one-way ANOVA and subsequent REGW test of the steepness coefficients of the regression lines (α). Comparison of the ED_{50}, ED_{90} and ED_{95} values between subgroups was performed using one-way ANOVA and subsequent REGW test.

Duration of action was defined as the interval between injection of the last neuromuscular blocking agent increment to 90% T1 recovery (T90) and to 70% T4/T1 recovery (TTOF70). T90 and TTOF70 were calculated on both the IEMG and MMG by linear intrapolation between the nearest neighbour measuring points [13].

In the current study, significant baseline drift with time was defined as failure of the IEMG T1 to recover to ≥ 90% of the pre-blocker T1 reference level, with T4/T1 > 0.90. In patients showing significant baseline drift with time, the IEMG-based T90 was considered as a missing value.

If, within the blocker groups, administration of the neuromuscular blocking agent was the same in each of the anaesthetic subgroups, T90 and TTOF70 values were compared between the anaesthetic subgroups by means of one-way ANOVA. The REGW test was applied subsequently to identify the source of difference.

Within the anaesthetic subgroups, IEMG-based ED_{50}, ED_{90}, ED_{95}, T90 and TTOF70 values were compared with the corresponding MMG-based variables using the two-tailed paired Student's *t* tests.

Statistical calculations were performed with the Statistical Applications Software of the SAS Institute (SAS/STAT Release 6.03, SAS Institute Inc, Cary, USA). All statistical tests were two-sided. $P < 0.05$ was considered to indicate statistical significance.

Results

We studied 108 patients, but the results from 18 were excluded because of measurement errors, technical failures or deviations from the study procedure. Within the blocker groups, there were no significant differences in age, weight, percentage of ideal weight for height or sex distribution between the anaesthetic subgroups (table 1).

The mean concentrations of isoflurane ($n = 30$) and sevoflurane ($n = 30$) were calculated to be 0.82 (SEM 0.01) MAC and 0.83 (0.01) MAC, omitting the MAC contribution of nitrous oxide, and 1.49 (0.02) MAC and 1.50 (0.01) MAC, respectively, including the MAC contribution of 70% nitrous oxide.

Within the blocker groups, the times of administration of the first (*t*1), second (*t*2) and third dose (*t*3) increments did not differ significantly between the anaesthetic subgroups (table 2).

Table 2 Times (mean (pooled SEM)) to cumulative dose administration after the initial dose: increments 1, 2 and 3 were injected at times T1, T2 and T3, respectively, in the different anaesthetic subgroups within the vecuronium, pancuronium and atracurium groups. NHA = No halogenated anaesthetic ($n = 10$), Iso = isoflurane ($n = 10$), Sev = sevoflurane ($n = 10$). Within the three blocker groups, there were no significant differences between the subgroups NHA, Iso and Sev for *t*1, *t*2 or *t*3

Group	Anaesthetic technique	*t*1 (min)	*t*2 (min)	*t*3 (min)
Vecuronium	NHA	5.8 (0.2)	9.8 (0.3)	12.9 (0.3)
($n = 30$)	Iso	6.1 (0.2)	10.0 (0.3)	13.2 (0.3)
	Sev	6.2 (0.2)	10.4 (0.3)	13.5 (0.3)
Pancuronium	NHA	6.2 (0.1)	10.0 (0.1)	13.2 (0.2)
($n = 30$)	Iso	6.3 (0.1)	10.4 (0.1)	13.9 (0.2)
	Sev	6.0 (0.1)	10.2 (0.1)	13.4 (0.2)
Atracurium	NHA	6.0 (0.1)	10.0 (0.2)	13.4 (0.2)
($n = 30$)	Iso	6.0 (0.1)	10.1 (0.2)	13.6 (0.2)
	Sev	6.1 (0.1)	10.4 (0.2)	13.9 (0.2)

Table 3 Steepness coefficients (mean (pooled SEM)) in the different anaesthetic subgroups within the vecuronium, pancuronium and atracurium groups. NHA = No halogenated anaesthetic ($n = 10$), Iso = isoflurane ($n = 10$), Sev = sevoflurane ($n = 10$). The steepness coefficients are the slopes of the regression lines, representing the relationship between the logit transformation of neuromuscular block and the logarithm of the dose. Neuromuscular block was assessed using either integrated electromyography (IEMG) or mechanomyography (MMG) as an effect variable. Within the three blocker groups, there were no significant differences between the subgroups NHA, Iso and Sev in steepness coefficients, as determined by either IEMG or MMG.

Group	Anaesthetic technique	Steepness coefficient	
		IEMG	MMG
Vecuronium	NHA	4.2 (0.2)	4.3 (0.3)
($n = 30$)	Iso	4.4 (0.2)	3.8 (0.3)
	Sev	4.2 (0.2)	3.7 (0.3)
Pancuronium	NHA	4.8 (0.2)	4.2 (0.2)
($n = 30$)	Iso	4.4 (0.2)	3.7 (0.2)
	Sev	4.5 (0.2)	3.6 (0.2)
Atracurium	NHA	5.1 (0.3)	4.8 (0.4)
($n = 30$)	Iso	4.6 (0.3)	4.3 (0.4)
	Sev	4.3 (0.3)	4.1 (0.4)

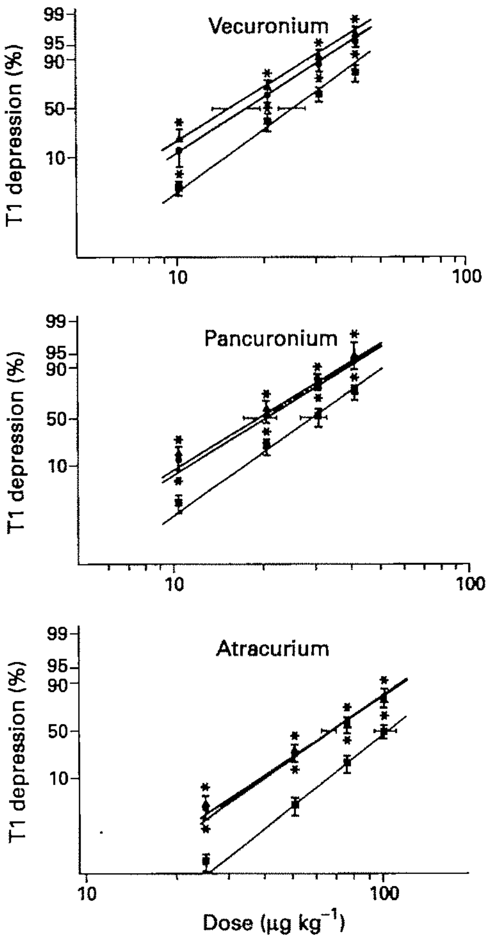


Figure 1 Mean cumulative dose–response relationships for vecuronium, pancuronium and atracurium in patients undergoing maintenance of anaesthesia in the subgroups: opioid–nitrous oxide–oxygen (NHA) (■); opioid–nitrous oxide–oxygen–isoflurane (Iso) (●) and opioid–nitrous oxide–oxygen–sevoflurane (Sev) (▲), consisting of 10 patients each. The logit transformation of the first twitch (T1) depression is plotted against the logarithm of the cumulative dose. The lines were obtained by linear least-squares regression. SEM are illustrated by horizontal (ED_{50}) and vertical error bars (T1 depression). *Significant difference ($P < 0.05$) compared with subgroup NHA. There were no significant differences between subgroups Iso and Sev.

Table 4 Cumulative dose–response data for vecuronium, pancuronium and atracurium in the different anaesthetic subgroups. NHA = No halogenated anaesthetic ($n = 10$), Iso = isoflurane ($n = 10$), Sev = sevoflurane ($n = 10$). ED_{50}, ED_{90}, and ED_{95} = doses producing 50%, 90% and 95% neuromuscular block, respectively, using either integrated electromyography (IEMG) or mechanomyography (MMG) as an effect variable (mean (pooled SEM)). *Significant difference ($P < 0.05$) compared with subgroup NHA. There were no significant differences between subgroups Iso and Sev; there were no significant differences between IEMG- and MMG-based variables

Group	Anaesthetic technique	ED_{50} (μg kg^{-1})		ED_{90} (μg kg^{-1})		ED_{95} (μg kg^{-1})	
		IEMG	MMG	IEMG	MMG	IEMG	MMG
Vecuronium	NHA	23.9 (1.7)	24.8 (2.0)	41.6 (3.4)	42.2 (2.9)	50.3 (4.6)	50.9 (3.6)
($n = 30$)	Iso	16.5 (1.7)*	16.9 (2.0)*	29.1 (3.4)*	30.3 (2.9)*	35.7 (4.6)*	37.1 (3.6)*
	Sev	15.0 (1.7)*	14.4 (2.0)*	25.8 (3.4)*	27.6 (2.9)*	31.2 (4.6)*	34.9 (3.6)*
Pancuronium	NHA	31.7 (1.3)	29.0 (1.4)	49.9 (1.7)	50.0 (1.8)	58.1 (2.1)	60.3 (2.3)
($n = 30$)	Iso	20.7 (1.3)*	20.3 (1.4)*	34.7 (1.7)*	37.2 (1.8)*	41.5 (2.1)*	45.9 (2.3)*
	Sev	21.3 (1.3)*	21.3 (1.4)*	35.0 (1.7)*	35.9 (1.8)*	41.6 (2.1)*	44.6 (2.3)*
Atracurium	NHA	117.0 (4.3)	112.4 (4.9)	187.0 (8.0)	177.7 (7.1)	218.7 (10.2)	207.6 (9.2)
($n = 30$)	Iso	67.8 (4.3)*	66.8 (4.9)*	109.6 (8.0)*	114.7 (7.1)*	129.2 (10.2)*	138.4 (9.2)*
	Sev	65.0 (4.3)*	66.5 (4.9)*	108.9 (8.0)*	117.1 (7.1)*	130.0 (10.2)*	142.6 (9.2)*

Table 5 Duration of action (mean (pooled SEM)) of vecuronium 40 µg kg^{-1}, pancuronium 40 µg kg^{-1} and atracurium 100 µg kg^{-1} in the different anaesthetic subgroups. NHA = No halogenated anaesthetic ($n = 10$), Iso = isoflurane ($n = 10$), Sev = sevoflurane ($n = 10$). T90, and TTOF70 = times to 90 % T1 and 70 % T4/T1 recovery, respectively, using either integrated electromyography (IEMG) or mechanomyography (MMG) as an effect variable. IEMG baseline drift = number of patients exhibiting failure of the IEMG T1 to recover to $\geq 90\%$ of the T1 reference level, with $T4/T1 > 0.9$. *Significant difference ($P < 0.05$) compared with subgroup NHA. There were no significant differences between subgroups Iso and Sev; there were no significant differences between IEMG- and MMG-based variables

Group	Anaesthetic technique	IEMG baseline drift	T90 (min)		TTOF70	
			IEMG	MMG	IEMG	MMG
Vecuronium ($n = 30$)	NHA	2	38.9 (6.1)	35.6 (5.7)	39.4 (4.3)	40.5 (5.4)
	Iso	3	60.1 (6.5)*	58.8 (5.7)*	62.4 (4.5)*	60.9 (5.4)*
	Sev	1	67.3 (5.7)*	58.1 (5.7)*	67.9 (4.1)*	70.5 (5.4)*
Pancuronium ($n = 30$)	NHA	1	57.9 (7.0)	57.4 (9.3)	60.5 (9.1)	67.1 (9.3)
	Iso	2	104.8 (7.3)*	111.6 (9.3)*	127.1 (9.7)*	135.8 (9.3)*
	Sev	4	93.1 (7.9)*	105.6 (9.3)*	118.5 (11.5)*	126.4 (9.3)*
Atracurium ($n = 30$)	NHA	0	28.2 (9.5)	25.9 (2.5)	28.7 (2.6)	30.5 (2.1)
	Iso	0	50.7 (9.5)*	50.3 (2.5)*	48.1 (2.6)*	50.1 (2.1)*
	Sev	1	49.6 (9.7)*	45.0 (2.5)*	50.8 (2.8)*	50.9 (2.1)*

For the blocker groups, the slopes of the cumulative dose–response curves did not differ significantly between the anaesthetic subgroups (table 3). The ED_{50}, ED_{90} and ED_{95} values, calculated for the subgroups Iso and Sev, were not significantly different. There was a significant difference in ED_{50}, ED_{90} and ED_{95} values ($P < 0.01$) between the subgroups receiving halogenated volatile anaesthetics (Iso and Sev) and the subgroup receiving opioid–nitrous oxide–oxygen anaesthesia (NHA) (table 4, fig. 1). There were no significant differences between the ED_{50}, ED_{90} and ED_{95} values determined using the IEMG or MMG.

In the blocker groups, T90 and TTOF70, measured for the subgroups Iso and Sev, were not significantly different. There was a significant difference in T90 and TTOF70 ($P < 0.01$) between the subgroups receiving the halogenated volatile anaesthetics and the subgroup receiving opioid–nitrous oxide–oxygen anaesthesia (table 5).

Fourteen patients exhibited significant IEMG baseline drift with time. Within the blocker groups, there were no significant differences between IEMG- and MMG-based T90 values for the patients exhibiting no significant baseline drift with time. Also, there were no significant differences between IEMG- and MMG-based TTOF70 values in all patients.

Discussion

We have demonstrated that equipotent concentrations of isoflurane and sevoflurane (i.e. 0.95 % and 1.70 %, respectively) augmented and prolonged vecuronium-, pancuronium- and atracurium-induced neuromuscular block to a similar degree compared with opioid–nitrous oxide anaesthesia. The concentrations of isoflurane and sevoflurane corresponded to 0.8 MAC, omitting the MAC contribution of nitrous oxide, and to 1.5 MAC, including the MAC contribution of 70 % nitrous oxide.

The current interaction study differed from previous ones [1–4] in that anaesthetic-related effects on neuromuscular blocking agents were compared within a carefully selected homogeneous population of young adults, using IEMG and MMG responses of the adductor pollicis brevis muscle simultaneously.

MAGNITUDE OF BLOCK

If administered in equipotent concentrations, inhalation anaesthetics enhanced vecuronium-, pancuronium- and atracurium-induced neuromuscular block to an approximately equal extent. The IEMG and MMG tend to detect similar magnitudes of block after administration of either vecuronium, pancuronium or atracurium. Similar observations have been made previously with tubocurarine [14]. The results of the current study are at variance with those of Engbæk and Roed [15] using pancuronium. Their findings may be explained by different conditions of anaesthesia, or recording electrode positioning [16] and stimulation frequency, or both [17].

The MMG-based potency estimates, assessed in the current study with an opioid–nitrous oxide–oxygen anaesthetic, were consistent with previously determined values for vecuronium [18, 19], pancuronium [20] and atracurium [18, 19] using the cumulative dose technique.

Our conclusions regarding the effect of isoflurane and sevoflurane on non-depolarizing neuromuscular block are in keeping with those of Morita and coworkers [3] who were unable to detect any significant difference between the potentiating effects of 1.15 % isoflurane and 2.05 % sevoflurane in 66 % nitrous oxide (i.e. 1 MAC of either vapour in oxygen–air without the MAC contribution of nitrous oxide) on neuromuscular block produced by vecuronium. However, the ED_{50}, ED_{90} and ED_{95} values calculated, using the single dose technique, were less than the current cumulative dose values. Redistribution between successive cumulative doses may explain the greater ED_{50}, ED_{90} and ED_{95} estimates in the current study. Moreover, the end-tidal concentrations of isoflurane and sevoflurane in their study (1.15 and 2.05 %, respectively) were approximately 20 %

higher than those used in the current study (0.95 and 1.70%, respectively). Additionally, there may be other factors (i.e. anthropometric, ethnic [21] or environmental [22]) that could have affected the sensitivity to vecuronium.

The cumulative dose technique, used in the current study, may underestimate the potency of the neuromuscular blocking agent with rapid distribution and elimination. However, administration of a neuromuscular blocking agent was consistent throughout the study and the volatile agent was chosen randomly; thus the degree of redistribution would have been similar in all patients within a blocker group undergoing maintenance of anaesthesia with different techniques. Additionally, the aim of the current study was to determine anaesthesia-related effects on non-depolarizing neuromuscular block and not to provide absolute potency estimates.

DURATION OF ACTION

In equipotent concentrations, both inhalation anaesthetics prolonged vecuronium-, pancuronium- and atracurium-induced neuromuscular block to a similar degree. The IEMG- and MMG-based TTOF70 values may be used interchangeably for the three neuromuscular blocking agent studied. Similar findings have been shown previously for atracurium [23] and tubocurarine [14]. However, during offset of neuromuscular block, IEMG T1 should be interpreted with caution as it may be unstable with time. The MMG-based T90 values assessed in the current study were comparable with previously published MMG T90 values during opioid–nitrous oxide–oxygen anaesthesia for vecuronium [24, 25], pancuronium [26] and atracurium [27] and during opioid–nitrous oxide–isoflurane anaesthesia for atracurium [27, 28].

Recent studies on the effect of sevoflurane on duration of vecuronium-induced neuromuscular block yielded data that showed wide variation on the extent of prolongation [2–4]. However, there were several methodological differences compared with our study. First, in these studies, patient ages ranged from 22 to 77 yr [2], 22 to 62 yr [3] and 25 to 75 yr [4], respectively. Second, offset of neuromuscular block was measured using the evoked IEMG, which was shown to be unreliable in 5–42% (18% in the current study) of patients [29]. As advancing age is associated with a greater incidence of slow recovery after vecuronium [5], and because the IEMG is unreliable during offset of non-depolarizing neuromuscular block [30], considerable between-patient variability in duration of neuromuscular block may have been produced within the populations studied. In the investigation of Saitoh, Toyooka and Amaha [2], the scatter in the duration of neuromuscular block, after the same dose of vecuronium ($0.2\ \mathrm{mg\ kg^{-1}}$) was so large that significant differences in the duration of neuromuscular block with opioid–nitrous oxide and opioid–nitrous oxide–isoflurane (end-tidal isoflurane concentration = 1.15%) anaesthesia could not be demonstrated. Therefore, comparison of such inaccurately determined recovery variables between these heterogeneous populations produces results that should be interpreted with caution.

Acknowledgements

We thank Marco de Wolff for his assistance and Theo de Boo for help with the statistical evaluation. This study was supported in part by a grant from Abbott Laboratories, Abbott Laboratories, Abbott Park, IL 60064, USA.

References

1. Tai K, Suzuki H, Itagaki T, Katsumara N, Nakamura T, Yamada M, Shiraishi H. Influence of sevoflurane on neuromuscular blocking effects of vecuronium and pancuronium. *Masui (Japanese Journal of Anesthesiology)* 1987; **36**: 227–232.
2. Saitoh Y, Toyooka H, Amaha K. Recoveries of post-tetanic twitch and train-of-four responses after administration of vecuronium with different inhalation anaesthetics and neuroleptanaesthesia. *British Journal of Anaesthesia* 1993; **70**: 402–404.
3. Morita T, Tsukagoshi H, Sugaya T, Yoshikawa D, Fujita T. The effects of sevoflurane are similar to those of isoflurane on the neuromuscular block produced by vecuronium. *British Journal of Anaesthesia* 1994; **72**: 465–467.
4. Nishiyama M, Mitani Y. Prolongation and recovery under sevoflurane anaesthesia of neuromuscular blocking action of vecuronium. *Masui (Japanese Journal of Anesthesiology)* 1994; **43**: 45–49.
5. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI II, Miller RD, de Jong RH, Elashoff RM. Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. *Anesthesiology* 1975; **42**: 197–200.
6. Scheller MS, Saidman LJ, Partridge BL. MAC of sevoflurane in humans and the New Zealand white rabbit. *Canadian Journal of Anaesthesia* 1988; **35**: 153–156.
7. Fragen RJ, Dunn K. Determination of the minimum alveolar concentration (MAC) of sevoflurane with and without nitrous oxide in elderly and young adults. *Anesthesiology* 1994; **81**: A361.
8. Poids moyen et ideal de l'adulte. In: Diem K, Lentner C, eds. *Tables Scientifiques*, 7th Edn. Basel: Ciba-Geigy, 1972; 717.
9. Quasha AL, Eger EI II, Tinker J. Determination and applications of MAC. *Anesthesiology* 1980; **53**: 315–353.
10. Takeda J, Ochiai R, Fukushima K. Recovery from vecuronium after different anaesthetics. *British Journal of Anaesthesia* 1994; **72**: 369–370.
11. *SAS/STAT User's Guide: Release 6.03*. Cary: SAS Institute Inc., 1989; 846.
12. Waud BE, Waud DR. On dose–response curves and anesthetics. *Anesthesiology* 1970; **33**: 1–4.
13. Atkinson K. Interpolation. In: Atkinson K, ed. *Elementary Numerical Analysis*, 2nd Edn. New York: John Wiley & Sons, Inc, 1993; 101–139.
14. Kopman AF. The effect of resting muscle tension on the dose–effect relationship of d-tubocurarine: does preload influence the evoked EMG? *Anesthesiology* 1988; **69**: 1003–1005.
15. Engbæk J, Roed J. Differential effect of pancuronium at the adductor pollicis, the first dorsal interosseous and the hypothenar muscles. An electromyographic and mechanomyographic dose–response study. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 664–669.
16. Kalli I. Effect of surface electrode position on the compound action potential evoked by ulnar nerve stimulation during isoflurane anaesthesia. *British Journal of Anaesthesia* 1990; **65**: 494–499.
17. Meretoja OA, Taivainen T, Brandom BW, Wirtavuori K. Frequency of train-of-four stimulation influences neuromuscular response. *British Journal of Anaesthesia* 1994; **72**: 686–687.
18. Smith CE, Donati F, Bevan DR. Cumulative dose–response

with infusion: A technique to determine neuromuscular blocking potency of atracurium and vecuronium. *Clinical Pharmacology and Therapeutics* 1988; **44**: 56–64.

19. Robertson EN, Booij LHDJ, Fragen RJ, Crul JF. Clinical comparison of atracurium and vecuronium (ORG NC 45). *British Journal of Anaesthesia* 1983; **55**: 125–129.
20. Stanley JC, Mirakhur RK. Comparative potency of pipecuronium bromide and pancuronium bromide. *British Journal of Anaesthesia* 1989; **63**: 754–755.
21. Houghton IT, Aun CST, Oh TE. Vecuronium: an anthropometric comparison. *Anaesthesia* 1992; **47**: 741–746.
22. Fiset P, Donati F, Balendran P, Meistelman C, Lira E, Bevan DR. Vecuronium is more potent in Montreal than in Paris. *Canadian Journal of Anaesthesia* 1991; **38**: 717–721.
23. Engbæk J, Østergaard D, Viby-Mogensen J, Skovgaard LT. Clinical recovery and train-of-four ratio measured mechanically and electromyographically following atracurium. *Anesthesiology* 1989; **71**: 391–395.
24. Krieg N, Crul JF, Booij LHDJ. Relative potency of Org NC45, pancuronium and tubocurarine in anaesthetized man. *British Journal of Anaesthesia* 1980; **52**: 783–788.
25. Donati F, Meistelman C, Plaud B. Vecuronium neuromuscular blockade at the orbicularis oculi and adductor pollicis muscles. *Anesthesiology* 1990; **73**: 870–875.
26. Katz RL. Clinical neuromuscular pharmacology of pancuronium. *Anesthesiology* 1971; **34**: 550–556.
27. Sokoll MD, Gergis SD, Mehta M, Ali NM, Lineberry C. Safety and efficacy of atracurium (BW33A) in surgical patients receiving balanced or isoflurane anesthesia. *Anesthesiology* 1983; **58**: 450–455.
28. Rupp SM, Fahey MR, Miller RD. Neuromuscular and cardiovascular effects of atracurium during nitrous oxide–fentanyl and nitrous oxide–isoflurane anaesthesia. *British Journal of Anaesthesia* 1983; **55**: 67S.
29. d'Hollander AA, Massaux F, Nevelsteen M, Agoston S. Age-dependent dose–response relationship of Org NC45 in anaesthetized patients. *British Journal of Anaesthesia* 1982; **54**: 653–656.
30. Smith DC, Hope T. Influence of serum concentrations of catecholamines and i.v. or volatile anaesthesia on evoked electromyography in the hand. *British Journal of Anaesthesia* 1994; **73**: 342–344.

British Journal of Anaesthesia 1996; **76**: 396–400

Performance assessment of a fuzzy controller for atracurium-induced neuromuscular block†

D. G. MASON, N. D. EDWARDS, D. A. LINKENS AND C. S. REILLY

Summary

The performance of a fuzzy controller for atracurium-induced neuromuscular block was assessed. Ten ASA I or II patients undergoing surgery anticipated to last at least 120 min were studied. A Datex Relaxograph was used to monitor neuromuscular block. Initially the T1 set point was set at 10% of baseline for at least 30 min (phase I). The T1 set point was then increased to 20% and then returned to 10% for two further periods of at least 30 min duration (phases II and III). The mean (SD) of the mean T1 error in 10 patients for phases I, II and III were 1.1 (1.4)%, −0.43 (1.2)% and 0.28 (0.94)%, respectively. The results show that a simple fuzzy logic controller can provide good accuracy with insensitivity to set point changes despite the considerable inter-individual variation in infusion rate required. (*Br. J. Anaesth.* 1996; **76**: 396–400)

Key words

Computers, fuzzy logic. Neuromuscular block, atracurium.

The provision of neuromuscular block is a fundamental part of anaesthesia. It is important that the degree of neuromuscular block is sufficient to provide adequate surgical conditions, while not so excessive as to make it difficult to antagonize at the end of surgery.

The degree of neuromuscular block is usually monitored by observing the muscle response to nerve stimulation, commonly the ulnar nerve. Bolus doses of neuromuscular blocker are usually administered intermittently based on this response. However, this method inevitably leads to fluctuations in the degree of neuromuscular block, particularly with recently introduced short-acting agents. To reduce this effect, continuous infusions of neuromuscular blocker may be used, but differences in pharmacodynamics and pharmacokinetics between patients make it difficult to choose the correct infusion rate to maintain the desired level of neuromuscular block [1]. Closed-loop control offers the ability to provide a stable level of neuromuscular block allowing for variations in individual responses to neuromuscular blocking agents.

Fuzzy logic control is a simple, although effective, technique for controlling non-linear and uncertain processes [2, 3]. The effect of neuromuscular blockers is non-linear and fuzzy logic provides a simple way to create a non-linear controller. Fuzzy logic accommodates uncertainty by dealing in imprecise, qualitative terms such as low, medium and high. This also provides control rules which are easy to understand and therefore simple to modify.

The derivation of the fuzzy rules is a common bottleneck in the application of fuzzy logic controllers. Conventionally, these fuzzy rules are based on emulating the control actions of an expert. Such a case was reported recently with the clinical application of fuzzy logic control to arterial pressure regulation using isoflurane [4]. However, with neuromuscular block no such experience is readily available to draw on for derivation of the fuzzy rulebase. This situation was the main driving force behind the introduction of self-organizing fuzzy logic controllers [5]. For this study, however, a fuzzy rulebase was hand-crafted based on a simulation involving the non-linear atracurium dose–response characteristic comprising pharmacokinetics and pharmacodynamics [5].

A particular configuration of fuzzy logic controller known as PD+I (proportional, differential plus integral) was found to be appropriate for this application via the use of computer simulation studies [5]. This fuzzy controller comprises separate PD and I components which correspond to dynamic and memory parts, respectively. The error signal (E) between the actual and desired TI value is processed first to form the differential ($D = dE/dt$) and integral (I) components. The error signal (E) gives the proportional component (P) directly. These error signals which are input to the fuzzy controller first need to be scaled to suit the particular control application. The separate outputs of the fuzzy PD and fuzzy I components also require scaling to suit the specific application. These input and output scaling factors for this fuzzy controller were identified by iterative computer simulations until good control performance was observed. We then assessed the performance of this fuzzy atracurium controller in clinical practice.

D. G. MASON, PHD, D. A. LINKENS, PHD, DSC(ENG) (Department of Automatic Control and Systems Engineering); N. D. EDWARDS, MB, BS, FRCA, C. S. REILLY, MD, FRCA (Department of Surgical and Anaesthetic Sciences); University of Sheffield, Mappin Street, Sheffield, South Yorkshire S1 3JD. Accepted for publication: October 11, 1995.

Correspondence to D.G.M.

†Presented in part at the Anaesthetic Research Society, Sheffield Meeting, July 7–8, 1995 (*British Journal of Anaesthesia* 1995; 75: 653P).

Subjects and methods

This study was approved by the local Ethics Committee. Ten ASA I or II patients undergoing surgery anticipated to last at least 120 min gave written informed consent.

The closed-loop system comprised an IBM compatible personal computer (PC) interfaced to a Datex Relaxograph for monitoring neuromuscular block and a Graseby Medical 3400 infusion pump for administration of atracurium. The PC was programmed to use the developed fuzzy control strategy and co-ordinate communication with the two devices via serial links. System safety was given close attention before commencing any clinical research. A hierarchical alarm structure was used so that any concurrently active alarm conditions were dealt with appropriately. System hardware and software integrity were monitored carefully offline in real-time using a simulation device attached to the Datex Relaxograph.

Patients received a standardized anaesthetic. After premedication with temazepam, anaesthesia was induced with alfentanil 10 mg kg^{-1} and a sleep dose of propofol followed by a propofol infusion of 10 mg kg^{-1} h^{-1}. The patient's lungs were then ventilated manually with nitrous oxide in oxygen while the automated drug delivery system was prepared. Stimulating electrodes for a Datex Relaxograph were placed over the ulnar nerve of the non-infused hand and sensing electrodes placed over the hypothenar area. The initial T1 set point was entered as 10% of baseline, a file name was entered for data storage and the concentration of atracurium (2 mg ml^{-1}) was entered so that the computer could convert the controller output from mass rate (mg h^{-1}) to volume flow rate (ml h^{-1}). In addition, the patient's weight was entered for calculation of the atracurium loading dose. When the computer system was satisfied that no alarm conditions were active, it delivered a loading dose of atracurium 0.33 mg kg^{-1} at 1200 ml h^{-1} to facilitate tracheal intubation. Anaesthesia was maintained with a propofol infusion of 8–10 mg kg^{-1} h^{-1}, the patient's lungs ventilated with 66% nitrous oxide in oxygen and morphine administered as appropriate. Neuromuscular block was controlled by the closed-loop fuzzy atracurium controller throughout the operation.

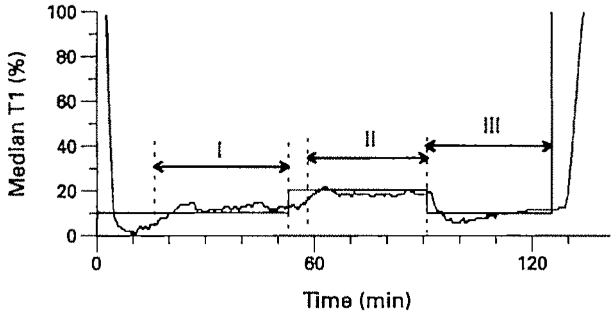


Figure 1 Sample clinical trace showing the definition of phases I, II and III used for the performance analysis. Note that these phases include transients.

The time taken after administration of the atracurium loading dose for T1 to start recovering and reach at least 5% of baseline was used to assess patient sensitivity to atracurium and thus determine its initial infusion rate. If this recovery time was fast (slow) the patient was judged insensitive (sensitive) to atracurium and therefore required a high (low) initial infusion rate. If T1 was above the initial 10% set point when neuromuscular block started to recover, the computer was programmed to give an additional 5-mg bolus over 3 min and repeat as necessary until T1 was less than the initial 10% T1 set point level. When T1 had recovered to 5–10%, the fuzzy controller commenced operation.

The fuzzy controller used the median of the last three T1 values. The Datex Relaxograph performed a train-of-four stimulation every 20 s to calculate the T1 error values at 1-min intervals which the fuzzy controller then used. The controller remained active at the initial 10% set point level for at least 30 min (phase I). The set point was then increased to 20% by keyboard entry and then returned to 10% again for two further periods of at least 30 min duration (phases II and III) (fig. 1). When the set point was reduced from 20% to 10%, an additional bolus dose of atracurium was administered equal to 10% of the value of the current mg h^{-1} integral (I) component of the fuzzy controller output. This was introduced to represent the situation where a prompt increase in neuromuscular block is required to improve surgical conditions while avoiding the problem of overshooting the degree of block required. During all phases the atracurium infusion rate was subject to an upper limit of 100 mg h^{-1}. In addition, the atracurium infusion was temporarily stopped if the median T1 value was more than 5% below the set point.

To assess the performance of the fuzzy controller, raw T1 values were analysed (i.e. not three-term median T1 values) to allow comparison of performance with previously reported controllers. T1 errors, defined as the raw T1 value minus the set point T1 value, were calculated for each phase with each patient. These T1 errors were analysed for each phase as follows: mean (SD); root mean square

Table 1 Control performance analysis (mean (SD) [range]) for the first 30 min of each phase only. This fixed period of analysis provides less variable, and therefore more meaningful, ISE and ITAE values

Phase	Mean error (%)	SD (%)	RMSD (%)	ISE (%) (min)	ITAE (min^2)	PC (%)
I	1.1 (1.4)	2.4 (0.68)	3.0 (0.62)	2.7 (1.1)	11 (2.5)	70 (22)
	[−0.9–2.9]	[1.7–3.6]	[2.0–4.2]	[1.2–5.0]	[7.0–14]	[34–89]
II	−0.43 (1.2)	1.5 (0.29)	1.9 (0.36)	1.1 (0.44)	6.7 (1.8)	39 (29)
	[−1.7–2.0]	[1.1–2.0]	[1.5–2.8]	[0.6–2.1]	[4.4–10]	[11–92]
III	0.28 (0.94)	3.4 (0.88)	3.5 (0.85)	3.2 (1.8)	8.4 (3.9)	47 (18)
	[−1.1–1.8]	[2.3–5.3]	[2.5–5.4]	[1.4–7.6]	[3.3–13]	[23–71]

deviation (RMSD); point count (PC), proportion of T1 errors above the T1 set point (i.e. those with positive value); integral square error (ISE); and integral time absolute error (ITAE) (appendix).

The latter two calculations are standard control engineering performance measures [6]. The first, ISE, is similar to RMSD, a measure of variation about the set point. The second, ITAE, is a measure which penalizes errors more heavily the further they are from the time origin of each phase. Both of these measures are sensitive to the period of analysis (appendix). We therefore selected the first 30 min of each phase for analysis. Clearly, for good control performance we need values for each of these calculations to be close to zero, except PC which needs to be close to 50%. Mean (SD) mg kg^{-1} h^{-1} atracurium infusion rates were also calculated for each phase. These values were then analysed for the 10 patients and expressed as mean (SD) and range.

Results

Ten patients (four male) were studied. Mean age was 59 (range 35–75) yr, mean weight 72 (45–110) kg. No phase III was possible for patient No. 4 because the operation ended earlier than expected. Mean duration of phase I was 45 (30–85) min, phase II 35 (28–57) min and phase III 47 (33–78) min. There was a wide range for duration of phases I and III. As some performance measures are sensitive to the magnitude of the period of analysis (appendix), we considered only the first 30 min of each phase.

Table 1 shows good control performance with a mean error of 1.1% and 0.28% above the 10% set point for phases I and III, respectively, and 0.43% below the 20% point for phase II. This is mainly consistent with the point count (PC) measure; more often above the set point in phase I with PC = 70%, more often below in phase II with PC = 39% and marginally more often below in phase III with PC = 47%. The SD values were 2.4%, 1.5% and 3.4% for phases I, II and III, respectively. This variation is low, particularly when it is considered that analysis includes transient phases. This implies that stable neuromuscular block was achieved. The SD and RMSD values were similar for each phase confirming that the mean error was close to zero. The ISE and RMSD performance measures are similar calculations and accordingly provide similar values for each phase. The ITAE performance measure was similar for phases I, II and III with values of 11, 6.7 and 8.4 min^2, respectively.

Table 2 Mean atracurium infusion rates for the 10 patients in the first 30 min of each phase only (mean (SD) [range])

Phase	Mean	SD
I	0.40 (0.08) [0.30–0.58]	0.23 (0.05) [0.16–0.30]
II	0.38 (0.10) [0.20–0.50]	0.22 (0.06) [0.10–0.32]
III	0.34 (0.08) [0.19–0.46]	0.22 (0.07) [0.12–0.35]

The range of the mean atracurium infusion rates which the fuzzy controller accommodated successfully in phases I, II and III were 0.30–0.58, 0.20–0.50 and 0.19–0.46 mg kg^{-1} h^{-1} (table 2). The SD was consistently high at 0.23, 0.22 and 0.22 mg kg^{-1} h^{-1} for phases I, II and III, respectively.

Discussion

Several different computer systems for feedback control of atracurium infusions have been reported. The periods used for performance analysis in these studies differ. Most have analysed only steady state performance [7–11]. We included transient phases in our performance analysis. Unlike previously reported clinical studies we tested the controller sensitivity to set point changes. Most studies have used EMG to monitor neuromuscular block. However, various different maintenance anaesthetics were used, some of which potentiate the effects of neuromuscular blockers. It is therefore not possible to provide a valid comparison of performance across these different atracurium controllers in terms of mean, SD and RMSD. However, there appears to be no statistically or clinically significant difference in reported controller performances. The main advantage the fuzzy controller offers over previously reported controllers is its simplicity and its friendly or intuitive designer interface. For example, a possible fuzzy control rule drawn from expert experience in the control of atracurium-induced neuromuscular block or just plain common sense could be:

> "IF T1 is greater than the set point by a LARGE amount
> AND T1 is moving towards the set point but only SLOWLY
> THEN set the atracurium infusion rate to a HIGH level."

The first line of this rule is a proportional (P) controller component, the second a differential (D) component. These antecedent components are fuzzy rule inputs. The final line is the fuzzy rule output.

This friendly designer interface for the fuzzy controller implies there is no need to understand complex mathematical formulae nor is there a need to interpret pharmacokinetic data. The fuzzy controller simply takes the T1 measurement and goes through some basic processing steps:

1. Input scaling

Scale each of the error inputs, that is proportional, differential and integral components.

2. Fuzzification

Assign fuzzy sets centred about these scaled values. This transforms error inputs from the real world to the fuzzy domain.

3. Fuzzy inferencing

Determine the degree of membership (DOM) of each error input with overlapping fuzzy sets. These calculated DOM values are used in combination with the fuzzy rules to calculate the DOM value for each fuzzy rule output.

4. Defuzzification

Combine the outputs of the fuzzy rules using a weighting method such as "centre of gravity". This transforms data from the fuzzy domain back to the real world.

5. Output scaling

This defuzzified value is scaled to give the real output value in terms of mg h^{-1} atracurium infusion rate.

Each of these steps requires simple calculations only. This low computational cost means it is simple to implement in terms of hardware and software.

The only other atracurium controller to report the point count (PC) performance measure also found that T1 was below a 20 % set point (our phase II) for most of the time (PC = 25 %) [9]. This may be a reflection of the non-linear atracurium dose–response characteristic in this region.

No previous clinical study has analysed the performance of an automated atracurium drug delivery system using ISE and ITAE but we report them here in the hope that future performance assessments will use them. It is noted that ITAE and ISE performance measures are sensitive to the duration of analysis (appendix). It is therefore important to compare these values over the same period (30 min in our study). The ISE is similar to the commonly reported RMSD as a measure of variation about the set point. However, ITAE has greater value because it measures the accuracy of the controller in reducing any error from the set point in proportion to the length of time as the controller commenced operation after receiving a new set point.

The consistently high SD atracurium infusion rate (table 2) indicates high controller activity, that is fluctuating infusion rates. This controller over-activity was not expected from computer simulation studies and suggests that the fuzzy PD (dynamic) component of the controller needed further testing with computer simulation under high system noise level conditions. Interestingly, however, Young and Hsiao [12] suggested that this pseudo-bolus action is required to promptly bring second compartment concentrations to desired levels in a three-compartment pharmacokinetic open model of neuromuscular blocking agents. The apparent over-activity of this fuzzy controller might be overcome by reducing the output scaling factor of the dynamic (PD) component of the fuzzy controller.

It may be argued that the fuzzy controller reported here could easily be implemented as a simple PID controller without the need for fuzzy logic. This would imply simply limiting the ranges for the PID error components in a piece-wise linear manner. This is true with this particular fuzzy controller but overlooks the potential for fuzzy logic controllers to provide a smooth and arbitrarily non-linear control surface with no additional computational burden. This holds particular promise with self-organizing fuzzy logic controllers which can modify the fuzzy rulebase online so as to match the needs of each individual patient, which may change during the course of an operation.

Clinically this system was useful. It provided stable surgical operating conditions, minimized the amount of neuromuscular blocker required by each patient, reduced the need for the anaesthetist to spend time controlling neuromuscular block, and allowed reliable antagonism of neuromuscular block at the end of surgery.

In conclusion, this simple fuzzy controller with fixed variables provided stable control of neuromuscular block and its performance was insensitive to set point changes.

Appendix

FORMULAE FOR PERFORMANCE ANALYSIS

The T1 error used for analysis was defined as follows:

$$E_n = T1_n - SP_n$$

where $T1_n$ = Relaxograph reading and SP_n = T1 set point for sample number n.

This error was then analysed in the following ways:

(i) Mean (M) and standard deviation (SD) of the T1 error,

$$M = \frac{\sum_{n=1}^{N} E_n}{N}$$

$$\mathrm{SD} = \sqrt{\frac{\sum_{n=1}^{N} (E_n - M)^2}{N-1}}$$

(ii) Root mean square deviation (RMSD) of T1 error,

$$\mathrm{RMSD} = \sqrt{\frac{\sum_{n=1}^{N} E_n^{2}}{N-1}}$$

(iii) Point count (PC), proportion of T1 samples above the T1 set point,

$$PC = \sqrt{\frac{N + \sum_{n=1}^{N} sgn(E_n)}{2 \times N}}$$

where $\mathrm{sgn}(E_n) = 1$ if E_n is > 0, else $\mathrm{sgn}(E_n) = -1$.

(iv) Integral square T1 error (ISE),

$$ISE = \int E_n^2 \times dt \approx \sum_{n=2}^{N} (E_n^2 \times (t_n - t_{n-1}))$$

(v) Integral time absolute T1 error (ITAE)

$$\mathrm{ITAE} = \int t \times |E_n| \times dt \approx \sum_{n=1}^{N} (t_n \times |E_n| \times (t_n - t_{n-1}))$$

References

1. Beemer GH. Continuous infusion of muscle relaxants—why and how. *Anaesthesia and Intensive Care* 1987; **15**: 83–89.
2. Asbury AJ, Tzabar Y. Fuzzy logic: new ways of thinking for anaesthesia. *British Journal of Anaesthesia* 1995; **75**: 1–2.
3. Martin JF. Fuzzy control in anaesthesia. *Journal of Clinical Monitoring* 1994; **10**: 77–80.

4. Zbinden AM, Feigenwinter P, Petersen-Felix S, Hacisalihzade S. Arterial pressure control with isoflurane using fuzzy logic. *British Journal of Anaesthesia* 1995; **74**: 66–72.
5. Mason DG, Linkens DA, Edwards ND, Reilly CS. Automated delivery of muscle relaxants using fuzzy-logic control. *IEEE Engineering in Medicine and Biology* 1994; **13**: 678–686.
6. Graham D, Lathrop RC. The synthesis of optimum transient response: criteria and standard forms. *AIEE Transactions on Applications to Industry* 1953; **72**: 273.
7. Assef SJ, Lennon RL, Jones KA, Burke MJ, Behrens TL. A versatile, computer-controlled, closed-loop system for continuous infusion of muscle relaxants. *Mayo Clinic Proceedings* 1993; **68**: 1074–1080.
8. Bradlow HS, Uys PC, Rametti LB. On-line control of atracurium induced muscle relaxation. *Journal of Biomedical Engineering* 1986; **8**: 72–75.
9. MacLeod, AD, Asbury AJ, Gray WM, Linkens DA. Automatic control of neuromuscular block with atracurium. *British Journal of Anaesthesia* 1989; **63**: 31–35.
10. Uys PC, Morrell DF, Bradlow HS, Rametti LB. Self-tuning, microprocessor-based closed-loop control of atracurium-induced neuromuscular blockade. *British Journal of Anaesthesia* 1988; **61**: 654–692.
11. Webster NR, Cohen AT. Closed-loop administration of atracurium: steady-state neuromuscular blockade during surgery using a computer controlled closed-loop atracurium infusion. *Anaesthesia* 1987; **42**: 1085–1091.
12. Young S, Hsiao K. A pharmacokinetic model to study administration of intravenous anaesthetic agents. *IEEE Engineering in Medicine Biology* 1994; **13**: 263–268.

British Journal of Anaesthesia 1996; **76**: 401–404

Comparison of arterialized venous with arterial blood propofol concentrations during sub-anaesthetic infusions in volunteers

K. R. JOHNSTON, M. D. VICKERS AND W. W. MAPLESON

Summary

We have compared propofol concentrations in arterial and arterialized venous blood (from the radial artery at the wrist and a vein in the opposite forearm) in five volunteers during a sub-anaesthetic increasing infusion regimen designed to produce pseudo-steady-state arterial concentrations of 0.06, 0.17 and 0.43 μg ml^{-1}. As in a previous study, we found no statistically significant difference between sampling sites ($P = 0.66$). However, changes in the method of arterialization yielded a reduction in the observed variability, with the arterialized venous propofol concentration lying within ±23% (95% reference interval) of the corresponding arterial concentration compared with 1 ±43%, as reported previously. (*Br. J. Anaesth.* 1996; **76**: 401–404)

Key words

Anaesthetics i.v., propofol. Measurement techniques, drug concentration. Pharmacology, steady-state infusions.

It is generally argued that studies on the uptake and distribution of anaesthetic agents and their effects on the central nervous system when administered by the i.v. or inhalation routes require estimation of the arterial concentration of the agents [1–3]. Relating central nervous system effects to arterial drug concentrations by repeated sampling presents ethical and practical difficulties in both patient and volunteer studies. The technique of arterialization, whereby forearm blood flow is increased by external heating to minimize the effect of tissue extraction and time lag, allows venous blood to be sampled as an alternative to direct arterial cannulation. The technique has been used previously for indirect estimation of arterial $P\text{CO}_2$ [4] and has been validated for halothane [3].

In a study of depression of the peak velocity of saccadic eye movements by sub-anaesthetic infusions of propofol in volunteers, Gao, Mapleson and Vickers [1] measured propofol concentrations in samples of arterialized venous blood as an alternative to arterial sampling. The measured concentrations differed substantially from predicted values and concern was expressed by the authors that some of the systematic deviation observed may have resulted from the site of blood sampling. Subsequently, direct comparison of arterialized venous and arterial blood propofol concentrations in a group of patients receiving similar, low-dose infusions was reported by Okell, Mapleson and Vickers [5]. The results of this study indicated that individual arterialized venous propofol concentrations may differ from corresponding arterial concentrations by as much as 1±43% (95% reference interval [6]). Such wide variability brought into question the acceptability of arterialized venous blood sampling as an investigative tool for propofol assay.

The present study was designed to evaluate the effect of improvement in the method of arterialization of forearm blood flow when comparing arterialized venous with arterial blood propofol concentrations during similar, sub-anaesthetic propofol infusions.

Subjects and methods

Approval was granted by the District Ethics Committee for the administration of sub-anaesthetic infusions of propofol in volunteers undergoing radial arterial cannulation for other research purposes. A medical questionnaire was completed, physical examination undertaken and written informed consent obtained from all participants. Each volunteer was weighed before administration of the propofol infusion. Five healthy, non-smoking volunteers (three male) completed the investigation.

INFUSION AND SAMPLING SITES

Using local anaesthesia, an 18-gauge cannula (1.2 mm o.d.) was placed in a suitable vein on the dorsum of the non-dominant hand for infusion of propofol.

For arterial blood sampling, a 20-gauge (1.0 mm o.d.) cannula (Venflon (R) 2 Viggo) was inserted using local anaesthesia into the radial artery of the same hand at the wrist. The cannula was connected via a short sampling line and three-way tap to a continuous flushing system (CFS Intraflo (R) II), pressurized with heparinized normal saline (1.0 u. ml^{-1}).

For sampling venous blood, a 14-gauge (2.0 mm o.d.) cannula was inserted using local anaesthesia into a large superficial vein of the dominant (arterialized) forearm, near the antecubital

---

K. R. JOHNSTON*, MB, BCH, FRCA, M. D. VICKERS, MB, BS, FRCA, W. W. MAPLESON, DSC, FINSTP, Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Cardiff CF4 4XN. Accepted for publication: November 2, 1995.

*Address for correspondence: Specialist Anaesthetist, Mount Gambia Hospital, PO Box 267, Mount Gambia, SA 5290, Australia.

Table 1 Sequence of administration of propofol to produce the three pseudo-steady-states. *Predicted arterial concentration at the end of each 25-min period

Infusion	Dose ($mg\ kg^{-1}\ h^{-1}$)	Duration (min)	Predicted concentration* ($\mu g\ ml^{-1}$)
(Bolus)	($0.03\ mg\ kg^{-1}$)	—	
1st	0.25	25	0.06
Loading	1.0	5	
2nd	0.6	20	0.17
Loading	2.3	5	
3rd	1.5	20	0.43

fossa. This cannula was connected to a source of heparinized saline via a sampling line and three-way tap. The ability to aspirate blood freely from the venous cannula without the use of a tourniquet or exposing the arm was confirmed at frequent intervals. The cannula was flushed periodically with 2-ml boluses of heparinized saline to maintain patency throughout the study period.

TECHNIQUE OF ARTERIALIZATION

The dominant arm was wrapped in an electric heating blanket in such a way that blood samples could be obtained without disturbing its position. No constricting bands were allowed on the sampling arm, which was placed horizontally at right angles to the body, as described previously [2, 3], to prevent venous obstruction. Forearm skin temperature was measured with a K-type (NiCr-NiAl) thermocouple (Digitron 1408-K) embedded in a bead of heat-conducting compound (RS55-431-1) and then taped to the skin with adhesive tape. The method used in a previous study by Okell, Mapleson and Vickers [5] raised questions as to the adequacy of "arterialization" because of the close proximity of the thermocouple and heating blanket. In order to ensure that we estimated true forearm skin temperature, for this study the thermocouple was insulated from the warming blanket by interposing polyurethane foam (5 × 5 × 2 cm) and adhesive aluminium foil. We assumed that venous blood had become arterialized when forearm skin temperature had increased to greater than 38 °C.

INFUSION REGIMEN

When arterialization of forearm blood had been achieved, the sub-anaesthetic infusion of propofol (Diprivan, Zeneca) was started using a syringe-driver type infusion device (Ohmeda 9000). The standard 1 % formulation ($10\ mg\ ml^{-1}$) was used; an initial bolus dose was followed by a stepwise increasing infusion regimen, identical to that used in previous studies [1, 2]. The infusion regimen (table 1) is based on a three-compartment computer model [7] using the pharmacokinetic microconstants reported by Gepts and colleagues [8]. This regimen is predicted to attain a pseudo-steady-state propofol concentration in the central compartment at the end of each of the three, 25-min periods. Appropriate allowance was made in the initial propofol bolus for the deadspace of the infusion system.

BLOOD SAMPLING AND ASSAY

At the end of each 25-min period, blood was obtained simultaneously from arterial and venous sampling cannulae, without the use of tourniquets. Appropriate deadspace volumes of blood were discarded (5 ml arterial and 10 ml venous). Each sample (venous and arterial) was divided into two identical aliquots, mixed with potassium oxalate and stored at 4 °C (a total of 12 aliquots per volunteer). Coded aliquots were assayed for blood propofol concentrations at another institution using high-pressure liquid chromatography with fluorescence detection, according to the method of Plummer [9]. The within-batch coefficient of variation (CV) reported for this method is 1.3–5.5 % and the between batch CV 2.9–12.3 %.

STATISTICAL ANALYSIS

Statistical analysis was by analysis of variance using Genstat 5, [10] release 1.3, running on a DEC mainframe computer under the Ultrix operating system OSF/1 V2.0B.

Analysis of variance was performed in terms of log concentration because this was needed to obtain similar variance at all three infusion rates, that is variability was consistent in terms of percentage of mean (coefficient of variation) rather than in absolute terms (SD). Analysis of variance distinguished four sources of variation: between subjects, between steady states, between sampling sites and between aliquots. The variations between steady states and between sampling sites were partitioned into systematic and random effects. The systematic effects were the differences between the mean concentrations for each steady state and for each sampling site.

Results

One outlying measurement (table 2) (50-fold higher than predicted) was treated as a "missing value" which Genstat handles appropriately. The analysis

Table 2 Measured whole blood propofol concentrations at the end of each 25-min period ($\mu g\ ml^{-1}$). *Outlier treated as missing value

		Concentration ($\mu g\ ml^{-1}$)			
Subject No.	Period	Arterialized venous		Arterial	
1	1	0.16	5.7*	0.25	0.20
	2	0.32	0.39	0.32	0.28
	3	0.60	0.54	0.63	0.62
2	1	0.15	0.16	0.11	0.15
	2	0.28	0.31	0.30	0.23
	3	0.58	0.69	0.70	0.66
3	1	0.12	0.12	0.15	0.13
	2	0.21	0.20	0.20	0.18
	3	0.49	0.61	0.51	0.43
4	1	0.13	0.13	0.15	0.15
	2	0.16	0.13	0.19	0.27
	3	0.57	0.70	0.45	0.49
5	1	0.12	0.14	0.14	0.15
	2	0.17	0.19	0.18	0.19
	3	0.39	0.44	0.43	0.37

Table 3 Analysis of variance of logarithms of the measured concentrations

Source of variation	Degrees of freedom	Sums of squares	Mean square	Variance ratio	P
Between					
Subjects (random)	4	0.28743	0.07186		
Steady states					
Systematic	2	3.29769	1.64885	134.4	< 0.001
Random	8	0.09814	0.01227		
Sampling sites					
Systematic	1	0.00155	0.00156	0.2	0.66
Random	14	0.10809	0.00772		
Between aliquots (random)	29	0.06989	0.00241		
Total	58	3.81743			

(table 3) shows that, although the three 25-min periods produced very different "steady state" concentrations ($P < 0.001$), the difference between sampling sites was not significant ($P = 0.66$).

From the mean squares in table 3, the SD between aliquots (the analytical error in terms of the log concentration) can be estimated [11] to be $\sqrt{0.00241} = 0.0491$ which, taking antilogs, corresponds to a coefficient of variation (CV) of 12.0%.

The mean difference in log concentration between sampling sites (mean arterialized venous − mean arterial) was −0.0102, that is −2.3%. The SD between sampling sites, after allowing for the contribution from analytical error, can be estimated [11] to be $\sqrt{\{(0.00772-0.00241)/2\}} = 0.0515$ which, again taking antilogs, corresponds to a coefficient of variation of 12.6%. The standard error of the difference of log concentration between the two sampling sites is then given by $0.0515 \times \sqrt{(2/15)} = 0.0188$, where 15 is the number of venous–arterial pairs in the study. From these results it can be calculated that the 95% confidence interval for the mean difference (arterialized venous − arterial) (av − a) is −11.0% to +7.2%, and that individual av − a differences may range (95% reference interval) [6] from −22.6% to +23.2%.

Discussion

Although the mean difference between arterialized venous and arterial concentrations was small and not significant, the confidence interval shows that the true mean difference might be of the order of 10% in either direction. Furthermore, the 95% reference interval shows that, in addition to the uncertainty arising from the analytical error, its concentration may (with 95% probability [6]) be between 23% less than the true arterial concentration and 23% greater.

Our previous study [5] also found a small, non-significant difference between arterialized venous and arterial concentration. The method of statistical analysis was slightly different from that used here; in particular, constancy of variance was achieved by expressing all measured concentrations as a percentage of the mean of the two arterial samples (in each set of two arterial and two venous). When those data were re-analysed in the same way as here (i.e. using log concentration) the mean arterialized venous concentration was further below the mean arterial concentration (−5.6% instead of our −2.3%) with a wider confidence interval (−17% to +7% compared with our −11% to +7%) and a much wider reference interval (−36% to +39% compared with our −23% to +23%). Therefore, it seems likely that the foam pad and foil, which were placed between the thermocouple and the warming blanket in this study, but not in the previous one [5], are essential.

Although the use of the foam pad reduced the scatter of the arterialized venous to arterial differences, the remaining 95% reference interval of ±23% must still imply that, at least at these low concentrations, measurement of arterialized venous concentration is of limited value in estimating the arterial concentration in an individual subject. However, it should be acceptable for mean concentrations measured in substantial numbers of subjects for research purposes. As found in previous studies [2, 4, 5], it is practicable to use the heating pad in patients.

The analytical error in the present study (CV of 12%) is at the upper limit of that claimed by Plummer [9] for the between-batch CV for the method and approximately twice that claimed for the within-batch CV, but very similar to the 11% found by Weaver and colleagues [12] for propofol concentrations up to 20 $\mu g\ ml^{-1}$ measured by the same method in sheep blood.

As found in the previous study [5], mean measured concentrations were greater than predicted: 0.15 (95% confidence interval 0.13–0.17) compared with a predicted value of 0.06; 0.23 (0.19–0.27) compared with 0.17; and 0.53 (0.45–0.63) compared with 0.43.

Acknowledgements

We acknowledge the assistance of Mr Mark Hampson, University of Wales College of Medicine, for technical support and the Sir Humphrey Davy Department of Anaesthesia, Bristol, for the propofol assays.

References

1. Gao F, Mapleson WW, Vickers MD. Effect of subanaesthetic infusions of propofol on peak velocity of saccadic eye movements. *European Journal of Anaesthesiology* 1991; **8**: 267–276.
2. Davies DN, Steward A, Allott PR, Mapleson WW. A comparison of arterial and arterialized venous concentrations of halothane. *British Journal of Anaesthesia* 1972; **44**: 548–550.

3. Major E, Aun C, Yate M, Savege TM, Verniquet AJW, Adam H, Douglas EJ. Influence of sample site on blood concentrations of ICI 35868. *British Journal of Anaesthesia* 1983; **55**: 371–375.
4. Harrison EM, Galloon S. Venous blood as an alternative to arterial blood for the measurement of carbon dioxide tensions. *British Journal of Anaesthesia* 1965; **37**: 13–18.
5. Okell RW, Mapleson WW, Vickers MD. Comparison of arterial and arterialized venous concentrations of propofol during infusion of propofol. *British Journal of Anaesthesia* 1991; **67**: 285–288.
6. Altman DG. *Practical Statistics for Medical Research.* London: Chapman and Hall, 1991; 419–426.
7. Arundel PA, Cockshott ID, Glen JB. Explicit: an interactive pharmacokinetics simulator for injectable anaesthetics. *British Journal of Anaesthesia* 1989; **63**: 230P.
8. Gepts E, Camu F, Cockshott ID, Douglas EJ. Disposition of propofol administered as constant rate infusions in humans. *Anesthesia and Analgesia* 1987; **66**: 1256–1263.
9. Plummer GF. Improved method for the determination of propofol in blood by high-performance liquid chromatography with fluorescence detection. *Journal of Chromatography* 1987; **421**: 171–176.
10. Genstat 5 Committee. *Genstat 5 Reference Manual.* Oxford: Clarendon Press, 1987; 389–449.
11. Davies OL, Goldsmith PL, eds. *Statistical Methods in Research and Production*, 4th Edn. London: Longmans, 1972; 161–162, 164–166.
12. Weaver BMQ, Staddon GE, Raptopoulos D, Mapleson WW. Measurement of propofol concentration in sheep blood and plasma: effect of storage at different temperatures. *Journal of Pharmacological and Toxicological Methods* 1995; in press.

British Journal of Anaesthesia 1996; **76**: 405–411

Radial artery tonometry: moderately accurate but unpredictable technique of continuous non-invasive arterial pressure measurement†

B. M. WEISS, D. R. SPAHN, H. RAHMIG, R. ROHLING AND T. PASCH

Summary

Radial artery tonometry provides continuous measurement of non-invasive arterial pressure (CNAP) by a sensor positioned above the radial artery. An inflatable upper arm cuff enables intermittent oscillometric calibration. CNAP was compared with invasive radial artery pressure recordings from the opposite wrist in 22 high-risk surgical patients with an inter-arm oscillometric mean arterial pressure difference ⩽ 10 mm Hg. Oscillometric, tonometric and invasive digital pressure values, and invasive and CNAP waveforms were obtained by the same instrument (Colin BP-508). Correlation coefficients (r) of invasive *vs* oscillometric values ($n = 481$ pairs) were 0.83, 0.90 and 0.92, and mean absolute errors of oscillometry were 7.6, 4.7, and 2.6 mm Hg for systolic, diastolic and mean arterial pressures, respectively. Correlation was poor for systolic ($r = 0.80$), diastolic ($r = 0.77$) and mean ($r = 0.84$) invasive *vs* CNAP values ($n = 1375$). Compared with oscillometry, mean absolute errors of 15.2, 10.9 and 9.4 mm Hg for systolic, diastolic and mean CNAP, respectively, were significantly ($P < 0.001$) higher. Mean prediction errors of CNAP, compared with invasive values, were −5.8 (SD 14.2) mm Hg for systolic, +7.2 (8.3) mm Hg for diastolic and +3.9 (8.8) mm Hg for mean arterial pressure. Individual patient accuracy of CNAP was assessed as good (individual prediction error ⩽ 5 (8) mm Hg and individual absolute error ⩽ 10 mm Hg) in seven patients, as acceptable (⩽ 10 (12) and ⩽ 15 mm Hg) in 11 patients, and as inadequate in four of 22 patients. Individual accuracy of oscillometry was good or acceptable in all 22 patients. The trend in CNAP changes (difference between consecutive measurements) was sufficiently accurate during induction of anaesthesia, as only 47 (7.6%), 14 (2.3%) and 27 (4.4%) of 616 systolic, diastolic and mean CNAP values differed by more than 10 mm Hg of invasive pressure trends. We conclude that: intermittent oscillometry provides accurate arterial pressure monitoring; CNAP measurements offer a reliable trend indicator of pressure changes during induction of anaesthesia and may be considered an alternative to invasive pressure measurements, should arterial cannulation be difficult in an awake patient; and accuracy of absolute CNAP values is only moderate and unpredictable, thus radial artery tonometry should not replace invasive monitoring in high-risk patients during major surgical procedures. (*Br. J. Anaesth.* 1996; **76**: 405–411)

Key words

Arterial pressure. Arterial pressure, measurement. Measurement technique, arterial pressure. Measurement techniques, tonometry. Measurement techniques, oscillometry.

The principles of tonometry are based on compressing and partial flattening (applanation) of a superficial artery against the underlying structures, preferably bone. The flattened surface of the arterial segment "balances" the pressure-induced circumferential stress on the arterial wall and the forces exerted by arterial pressure become perpendicular to wall tension. The ongoing intra-arterial forces, sensed by a pressure transducer attached firmly on the skin surface above the artery, are translated into arterial pressure waveforms [1, 2]. Radial artery tonometry was incorporated recently in anaesthesia monitoring instruments. Using an inflatable upper arm cuff, the calibration (oscillometry) for tonometric pressure values is provided intermittently. In addition to oscillometric pressure, continuous non-invasive arterial pressure (CNAP) waveform and tonometric digital pressure values are displayed continuously and updated automatically. In anaesthetized patients, the method was found to provide accurate, reliable online information, even during induced hypotension [3, 4]. Other investigators reported poor accuracy of radial artery tonometry and limited ability to detect significant changes more rapidly than with oscillometry alone [5]. Also, a limited ability to capture the pulse pressure signal in

---

BRANKO M. WEISS, MD, DONAT R. SPAHN, MD, HARALD RAHMIG*, MD, ROMAN ROHLING, MD, THOMAS PASCH, MD, Department of Anaesthesiology, University Hospital Zürich, CH-8091 Zürich, Switzerland. Accepted for publication: October 28, 1995.

*Present address: Department of Anaesthesiology, Klinikum Ludwigsburg, D-71640 Ludwigsburg, Germany.

†Presented in part at the Annual Congress of the European Society of Anaesthesiologists, Paris, 1995 (*British Journal of Anaesthesia* 1995, 74 (Suppl. 1): A28).

Correspondence to B.M.W.

paediatric patients was observed [6]. An accurate technique of CNAP measurement, however, could replace invasive arterial pressure monitoring in some patients, avoiding the risks of arterial cannulation. In addition, arterial cannulation can be difficult in the awake state, and CNAP monitoring may be a temporary alternative, allowing cannulation later under the more favourable condition of general anaesthesia.

The purpose of the study was to evaluate radial artery tonometry in patients with concomitant cardiac, vascular, pulmonary and renal diseases undergoing non-thoracic surgical procedures.

Patients and methods

The study was approved by the Institutional Ethics Committee. After obtaining informed consent, we studied patients undergoing abdominal or transurethral surgical procedures in the supine or lithotomy position, requiring invasive arterial pressure monitoring with no history of recent radial artery cannulation. The anaesthetic technique was chosen independent of the investigation. Premedication comprised oral midazolam and patients were placed in the supine position on an operating table. A circulating water mattress and warmed i.v. infusions were used to maintain normothermia. The arms were placed on armholders at the level of the heart, abducted approximately 45–70° from the body. Arterial pressure was measured oscillometrically on both arms, using an adult size, inflatable upper arm cuff and a multifunctional monitoring instrument (BP-508, Colin Medical Instrumentations, Komaki, Japan). Three patients with an inter-arm mean arterial pressure difference exceeding 10 mm Hg (average of three measurements) were excluded. Patient characteristics (19 males and three females), inter-arm oscillometric differences and concomitant diseases are summarized in table 1.

A radial artery cannula (20-gauge, 32 mm) was inserted during local anaesthesia and connected to low compliance tubing (diameter 1.0–1.5 mm, length 165 cm, two stopcocks). A disposable pressure transducer (Deltran, Utah Medical, Midvale, UT, USA) was used. This set was tested previously *in vitro* with a pressure waveform generator. Almost identical values for mean and trough pressure were found, and peak pressure was overestimated by a mean of 2.0 (SD 0.8) mm Hg, compared with values obtained by a micromanometer pressure transducer [7]. The pressure transducer was connected to the pressure module (with a low-pass filter for frequencies greater than 25 Hz) of the Colin instrument. The level of the right atrium was used for zero calibration.

Table 1 Patient characteristics ($n = 22$) (mean (SD) [range])

Age (yr)	66.3 [25.5–91.1]
Weight (kg)	74.0 (14.3) [42.5–91.0]
Height (cm)	172 (7) [155–182]
Inter-arm pressure difference (mm Hg)	
Systolic	0.1 (6.9) [−4.3–14.3]
Diastolic	1.4 (6.4) [−6.7–15.7)]
Mean	3.0 (6.2) [−9.6–10.0]
Concomitant diseases (*n*)	
Coronary artery disease	11
Arterial hypertension	9
Chronic heart failure	6
Cardiac arrhythmias	3
Valvular heart disease	1
Peripheral vascular disease	5
Cerebrovascular disease	4
Diabetes mellitus	4
Chronic lung disease	5
Renal insufficiency	5

The upper arm cuff and the housing with a multi-element array sensor (SA-250, Colin, Komaki, Japan), attached above the radial artery, were placed on the contralateral arm. The dimensions of the sensor housing were 7.0 × 4.0 × 3.7 cm, with weight 90 g. The wrist was placed in a brace in an extended position and the brace and sensor housing were wrapped, as recommended by the manufacturer. The intermittent oscillometric measurements served as the reference (occlusive calibration) and defined the range and values for tonometric CNAP. Automatic recalibration occurred independently of the preset interval whenever the device registered distortion of the CNAP curve. The instrument displayed on the screen: digital oscillometric pressure values, selected time interval and time elapsed since the previous calibration; invasive and CNAP curves on the same scale; and synchronously, the updated invasive and tonometric digital values for systolic, diastolic and mean arterial pressures. One of the 30 elements of the sensor transducer identified automatically maximal pulse amplitude signals from the flattened radial artery. A small graphical display (tonogram) on the screen indicated the position of the "active transducer" as a vertical line and as a bar. Within given limits, automatic repositioning of the active element–transducer and optimal pulse amplitude identification occurred, otherwise manual repositioning was required. Another graphical display and digital value indicated so-called signal strength. Signal strength is calculated automatically by the device as the ratio between the peak-to-peak amplitudes of tonometric pressure to the amplitudes of cuff oscillations. According to the manufacturer, signal strength should be 50–100 amplitude units. Inadequate sensor placement and a signal strength less than 50 amplitude units required repositioning of the sensor. The pressure applied on the wrist by the sensor (hold-down pressure), controlled through a microprocessor and set by a pneumatic bladder within the housing, was displayed on the screen. Initial signal strength and hold-down pressure values were recorded in each patient, and controlled throughout the procedure.

Comparative measurements were started before induction of anaesthesia and lasted until the patient was prepared to leave the operating room. Oscillometric calibration was preset at 5-min intervals during induction of anaesthesia and at 10-min intervals for the rest of the procedure. Invasive and tonometric CNAP values were documented every 30–60 s during induction of anaesthesia and every 3–5 min for the remainder of the procedure. The built-in printer automatically and continually recorded the time of day and a pair of oscillometric and invasive pressure values *or* a pair of invasive and tonometric CNAP values. All values were later checked and incomplete or artefactual pairs (collected during blood aspiration, flushing, repositioning of the sensor or unstable signal strength) were excluded from analysis. As the waveform recording was not provided by this instrument software, both CNAP and invasive pressure curves were printed continually on a multichannel paper recorder (Servomed, Hellige, Freiburg, Germany). The oscillometric signal and scale could not be recorded, and the CNAP trace was centred manually within the channel and the amplitude adjusted to that of invasive pressure.

The time periods of induction of anaesthesia and surgical procedure, actual time interval between oscillometric calibrations and actual frequency of CNAP collection were recorded for each patient. Invasive pressure was considered the reference. Oscillometric and corresponding invasive pressure pairs and, separately, tonometric CNAP and corresponding invasive pressure pairs were analysed. Pressure differences were calculated for each pair of systolic, diastolic and mean values. Mean (SD) pressure differences (prediction error or bias) were derived for oscillometry and tonometry, cumulatively for all data and individually for each patient. Absolute error (precision) was calculated as the sum of squared pressure differences, divided by the number of measurements, cumulatively for all data and individually for each patient [8]. Percentage error was derived from (mean pressure difference/mean of average pressure) × 100. Oscillometric and tonometric errors were compared by the Student's *t* test and $P < 0.05$ was considered statistically significant. To evaluate the correlation between the measured and calculated variables, linear regression analysis, with coefficient of correlation (*r*) and 95 % confidence intervals for the single observations, was used. The average pressure of each pair and the mean of the average were calculated for oscillometric and invasive, and for tonometric and invasive pairs. Each tonometric prediction error was plotted against the average pressure value of the two measurements, and the mean error (bias) and limits of agreement (±2 SD) were drawn [9]. Each patient's individual prediction error of tonometric and oscillometric systolic, diastolic and mean arterial pressure was defined arbitrarily as good ($\leqslant 5$ (8) mm Hg), acceptable (5 (8) < errors $\leqslant 10$ (12) mm Hg) or poor (> 10 (12) mm Hg). Individual mean absolute errors of $\leqslant 10$, 11–15 and > 15 mm Hg were arbitrarily classified as good, acceptable and poor, respectively. Bias and precision of systolic, diastolic and mean arterial pressures were combined to assess oscillometry and, separately, tonometry in each patient, according to an arbitrary score (two errors for three pressures: 2 = good, 1 = acceptable and 0 = poor error). Good monitoring required a score of 9–12 points, acceptable monitoring 5–8 points, and 0–4 points indicated a poor function of tonometric CNAP. A pressure difference between two consecutive measurements (trend of changes) was derived for the invasive and CNAP methods during induction of anaesthesia. The critical difference between the two trends was arbitrarily set at 10 mm Hg. Data are presented as mean (SD) unless otherwise stated.

Results

The mean period of measurement was 153 (87) min and the mean duration of surgery 109 (75) min. We studied five patients during spontaneous breathing, using regional anaesthesia in two patients and general anaesthesia in three. General anaesthesia, neuromuscular block and controlled ventilation were used in 17 patients, in seven patients combined with a continuous extradural block. Single or multiple i.v. injections of ephedrine, nitroglycerin, or both, were given to 12 patients, one patient received a dopamine infusion of 1–3 $\mu g\ kg^{-1}\ min^{-1}$ for 2.5 h, and in nine patients vasoactive drugs were not given. Intraoperative blood loss was estimated as less than 10 % of circulating blood volume in 13 patients, less than 20 % in two patients, less than 50 % in three patients and exceeding 50 % in four patients. Blood volume was substituted, as required, with crystalloid and colloid solutions, and blood transfusions.

According to the tonogram, and axial and signal strength indicators, correct sensor positioning was obtained initially in all patients. Initial values of signal strength and hold-down pressure were 96.5 (21.8) amplitude units and 78.0 (32.7) mm Hg, respectively. Protection of the sensor position, as a result of the abducted arm and the weight and volume of the sensor housing itself, was found to be difficult on occasion. In several patients repositioning of the sensor was required during the study. In one patient tonometric CNAP ceased to function, the warnings and repeated oscillometric measurements indicated a function failure, and then CNAP monitoring returned automatically. The function of the device was not disturbed by the intraoperative use of electrocautery. The CNAP curve looked acceptable, compared with the simultaneous invasive pressure curve, during normal heart rate and cardiac arrhythmia.

We analysed a total of 481 pairs of oscillometric and invasive pressure (21.9 (12.6) pairs per patient), and 1375 pairs of tonometric and invasive pressure (62.5 (28.4) pairs per patient). During induction of anaesthesia (30.7 (18) min) and for the remainder of the procedure, oscillometric calibration was performed every 6.1 (3.1) min and 8.5 (2.5) min, respectively, and tonometric CNAP data were collected every 1.0 (0.5) min and 4.7 (2.0) min, respectively. Pressure differences and dispersion of errors showed a normal distribution. Cumulatively (table 2), oscillometric measurements were more accurate than tonometric CNAP. Absolute errors of CNAP were significantly larger than corresponding absolute errors of oscillometry. Average CNAP errors and linear regression analysis (*r*, mean prediction line) of the pooled data showed small discrepancies and a significant correlation with invasive pressure values. The confidence interval range, however, exceeded 50 mm Hg for systolic and 30 mm Hg for diastolic and mean (fig. 1) arterial pressures. The limits of agreement (2 SD) between

Table 2 Cumulative analysis of non-invasive *vs* invasive arterial pressure values (mean (SD)). ***$P < 0.001$ *vs* corresponding oscillometric errors

	Oscillometry ($n = 481$)			Tonometry (CNAP, $n = 1375$)		
	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean
Correlation (r)	0.83	0.90	0.92	0.80	0.77	0.84
Prediction error	−2.2	+8.8	+4.4	−5.8	+7.2	+3.9
(bias) (mm Hg)	(12.8)	(5.1)	(6.2)	(14.2)	(8.3)	(8.8)
Average pressure	122.4	+66.2	85.2	121.0	64.2	83.7
(mm Hg)	(20.4)	(7.8)	(14.3)	(20.4)	(11.5)	(14.9)
Percentage error	−1.8	+13.3	+5.2	−4.8	+11.1	+4.6
of average (%)	(10.4)	(7.8)	(7.2)	(11.8)	(12.9)	(10.6)
Absolute error	7.6	4.7	2.6	15.2***	10.9***	9.4***
(precision) (mm Hg)	(5.1)	(3.1)	(1.9)	(4.7)	(3.0)	(3.4)

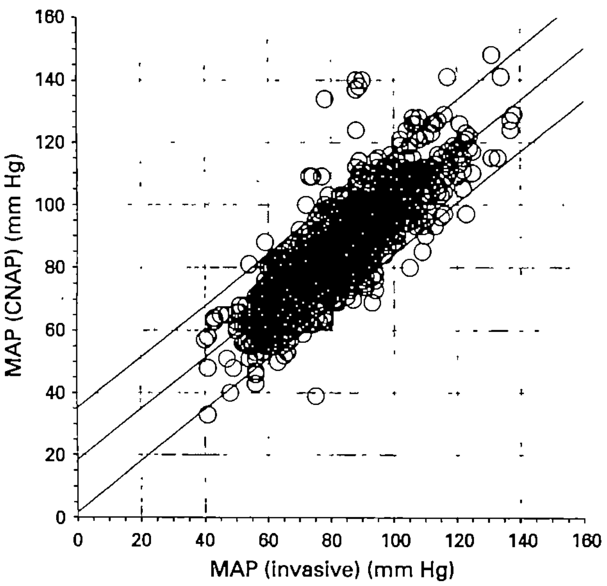


Figure 1 Linear regression analysis with scatterplot for mean arterial pressure (MAP) of the invasive *vs* the CNAP method ($n = 1375$, $r = 0.84$). Mean prediction line and 95% confidence intervals for the single observations, with a range of 33 mm Hg, are shown.

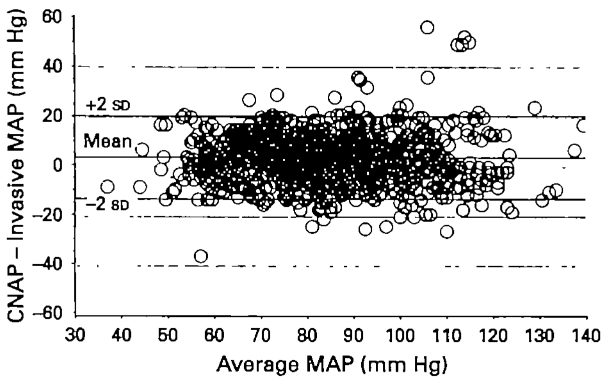


Figure 2 Scatterplot of pressure differences and average pressure for mean arterial pressure (MAP) of the invasive *vs* the CNAP method ($n = 1375$). Mean prediction error (bias) and limits of agreement (2 SD = 16.5 mm Hg) between the two methods are shown, according to Bland and Altman [9].

the invasive and CNAP methods exceeded 54 mm Hg for systolic and 30 mm Hg for diastolic and mean (fig. 2) arterial pressures.

According to individual bias and precision of oscillometry, 14 (11%) of 132 (two criteria, three pressures, 22 patients) values were in the poor category. Globally, intermittent non-invasive monitoring was assessed as good in 16 and as acceptable in six patients. According to each patient's individual bias and precision of tonometry, 50% of systolic values showed poor accuracy, diastolic values were predominantly in the acceptable category and the majority of the mean CNAP values showed good agreement with invasive measurements (table 3). CNAP monitoring was assessed as good in four patients, acceptable in 14 and poor in four of 22 patients. These four patients with inadequate tonometric accuracy could not be distinguished from the other 18 patients in terms of concomitant diseases, inter-arm oscillometric pressure difference (in one case it was among the lowest of all patients), bias and precision of oscillometry, course of the procedure (blood loss, vasoactive drugs) and sensor performance (signal strength, hold-down pressure). Individual inter-arm pressure difference did not correlate with individual oscillometric ($r = 0.13$) or tonometric ($r = 0.25$) prediction errors. A strong correlation between oscillometric and tonometric prediction errors ($r = 0.86$, fig. 3), and a moderate correlation between oscillometric and tonometric absolute errors ($r = 0.48$) were found, but the confidence interval range for both analyses exceeded 15 mm Hg.

The correlation of trends in mean arterial pressure changes with the invasive and CNAP methods ($n = 616$, 28 (16) pairs per patient) during induction of anaesthesia showed a confidence interval range within 20 mm Hg (fig. 4). The difference between the two trends exceeded 10 mm Hg in 47 (7.6%) measurements for systolic pressure in 16 patients, in 14 (2.3%) measurements for diastolic pressure in seven patients and in 27 (4.4%) measurements for mean arterial pressure in 12 patients. These discrepancies occurred predominantly in one of 22 patients.

Discussion

Comparison of non-invasive and invasive arterial pressure methods results inevitably in disagreement [10]. Measurements at different arterial sites are confounded by differences in velocity of pressure wave propagation, unequal impedance, reflections and resonances, in addition to differences in blood

Table 3 Accuracy of tonometric CNAP according to each patient's individual prediction error (bias) and individual absolute error (precision). *Prediction error of ≤ 5 (8) mm Hg was arbitrarily defined as good, 5 (8) < error ≤ 10 (12) mm Hg as acceptable and > 10 (12) mm Hg as poor. Absolute errors of ≤ 10, 11–15 and > 15 mm Hg were defined correspondingly. Data are number of patients (%) for each category (total = six criteria in 22 patients = 132 (100%))

	Prediction error (bias)			Absolute error (precision)			
Definition*	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean	Total
Good	1 (5)	2 (9)	14 (64)	3 (14)	8 (36)	16 (72)	44 (33)
Acceptable	9 (41)	16 (73)	5 (23)	8 (36)	11 (50)	5 (23)	54 (41)
Poor	12 (54)	4 (18)	3 (13)	11 (50)	3 (14)	1 (5)	34 (26)
Patients	22 (100)	22 (100)	22 (100)	22 (100)	22 (100)	22 (100)	132 (100)

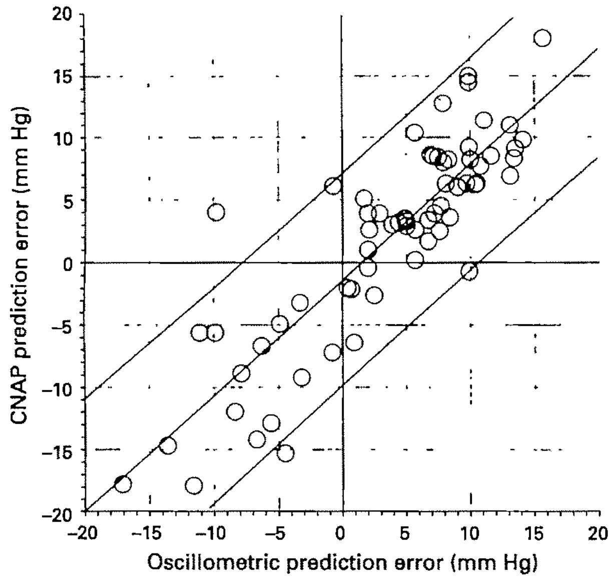


Figure 3 Linear regression analysis with scatterplot of individual oscillometric mean prediction error *vs* individual tonometric (CNAP) mean prediction error for systolic, diastolic and mean arterial pressures ($n = 66$, $r = 0.86$). Mean prediction line and 95% confidence intervals for single observations, with a range of 17 mm Hg, are shown.

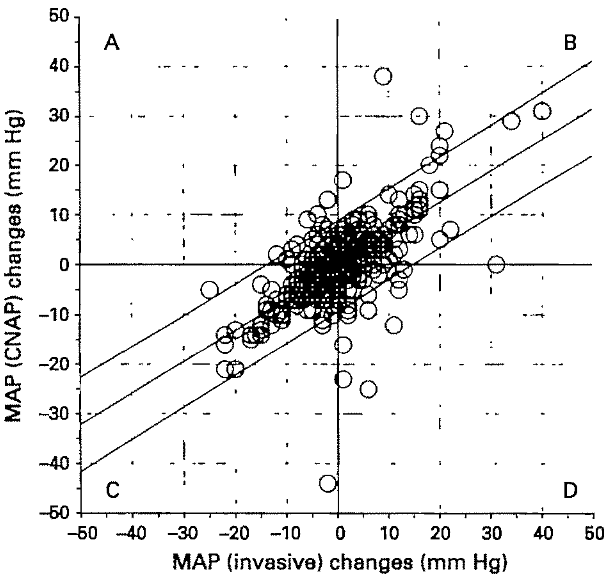


Figure 4 Linear regression analysis with scatterplot of trends in mean arterial pressure (MAP) changes (difference between consecutive measurements) for the invasive and CNAP methods during induction of anaesthesia ($n = 616$, $r = 0.66$). Mean prediction line and 95% confidence intervals for the single observations, with a range within 20 mm Hg, are shown. Data in the B and C quadrants indicate the changes in the two methods in the same direction, and data in the A and D quadrants indicate changes in the opposite direction. In 27 instances (4.4%), predominantly in one of 22 patients, the difference between the two trends exceeded 10 mm Hg.

flow distribution within the arterial system [11]. Furthermore, the basic principles of non-invasive methods share no similarities with, and only superficially resemble, the invasive method [1–6, 10, 12–14]. Although the intra-arterial measurement should theoretically be considered the "gold standard", its precision is dependent on a variety of technical factors [3–7, 10–17]. Also, numerous, poorly controlled patient variables, external influences and cardiocirculatory changes during a dynamic period of anaesthesia and surgery further accentuate the difference between the methods of pressure measurement [3–6, 10–24]. As a rule, pressure values from different methods over time show bidirectional variations in one subject and even more variation when the data are summarized for a group of patients. Different principles of measurement at different arterial sites, and different types of capturing, speed and interpretation of "pressure signals" explain the absence of exclusive or even predominant pressure over- or underestimation by a non-invasive method. The present study indicates that, compared with contralateral invasive radial artery pressure: intermittent oscillometry provides accurate arterial pressure monitoring; CNAP measurements by radial artery tonometry offer a reliable trend indicator of pressure changes during induction of anaesthesia; radial artery tonometry may be considered a valid alternative to invasive pressure measurements, if arterial cannulation is difficult in an awake patient; and accuracy of absolute CNAP values is only moderate and unpredictable, thus it should not replace invasive monitoring in high-risk patients during major surgical procedures.

Other CNAP methods (finger photoplethysmomanometry, dual photometry and pulse wave-delay, brachial artery displacement) have been evaluated previously during anaesthetic and surgical procedures [23–29]. Using various criteria, each method has been shown to be insufficiently accurate for most subjects or for most of the time, or both, and none could be recommended as an alternative to invasive pressure monitoring. Radial artery tonometry had promise as an accurate and simple method of CNAP recording, with narrow limits of agreement and high precision compared with simultaneous invasive measurements [1]. A high level of accuracy was obtained during controlled hypotension but invasive pressure was measured in some cases with a resonance overshoot eliminator, without explaining the reasons and criteria for its use [4]. Such a device has not been tested adequately under clinical conditions [7, 16, 17], and thus cannot be considered a requirement for high-fidelity reproduction of invasive arterial pressure. More recently, Siegel, Brock-Utne and Brodsky analysed a large number of invasive and tonometric CNAP pairs, and reported discrepancies between invasive and CNAP readings [5]. These authors concluded that tonometric CNAP is unable to detect changes in arterial pressure more rapidly than intermittent oscillometry, as accuracy of the tonometric sensor is limited.

For this investigation, a mixed group of high-risk surgical patients, undergoing various non-thoracic surgical procedures, was selected for testing tonometric CNAP. Both non-invasive methods, oscillometry and tonometry, on average underestimated systolic and overestimated diastolic and mean arterial pressures. Compared with intermittent oscillometry, radial artery tonometry exhibited inferior accuracy. By pooling (mixing of all "good and bad" data) and cumulatively analysing all pressure pairs, the coefficients of correlation, mean prediction and percentage errors (2–9 mm Hg and 2–13 %, respectively) of oscillometry and tonometry indicated almost excellent agreement with invasive radial artery pressure. These data alone, however, may not reveal a bidirectional spread and real discrepancy of non-invasive *vs* invasive values. One and 2 SD of the errors, and 95 % confidence intervals revealed some disagreement for all patients (table 2, figs 1, 2). Using the absolute error (precision), a rigorous and overall indicator of accuracy, oscillometry showed a narrow SD range of 1–13 mm Hg for systolic, diastolic and mean arterial pressures. Aware of inherent limitations of a CNAP method, the cumulative tonometric precision with an SD range of 6–20 mm Hg could eventually indicate that radial artery tonometry is a clinically useful technique during anaesthesia and surgery.

Standards for non-invasive arterial pressure measuring devices and specific requirements during anaesthesia are inadequately defined. They are extrapolated from studies in healthy volunteers or non-surgical patients under steady-state conditions. The American National Standard of the Association for the Advancement of Medical Instrumentation recommended that the maximal bias of non-invasive arterial pressure, obtained from at least 85 patients, should not exceed 5 (8) mm Hg from a non-invasive reference method [30]. The British Hypertension Society expanded the procedure for evaluation of arterial pressure measuring devices, and considered the 5 (8)-mm Hg criterion too liberal. A grading system was proposed according to the percentage of readings ⩽ 5, ⩽ 10 and ⩽ 15 mm Hg from a non-invasive reference method [31]. Both standards and procedures are not applicable directly to anaesthesia and the intraoperative environment, and both are too rigorous (albeit theoretically desirable) for evaluation of a non-invasive (*vs* invasive) method of arterial pressure measurements. In this study only the mean pressure value measured oscillometrically (table 2) fulfilled the American standard for minimal bias (SD) [30]. Adopting the British criteria [31], even oscillometric mean arterial pressure (with 50 % of pressure differences within 5 mm Hg and 84 % within 10 mm Hg) would be only partially acceptable.

Another approach to the evaluation of non-invasive techniques was considered necessary. To provide more insight into the individual performance of oscillometry and tonometry, the data were pooled and analysed separately for each patient (instead of pooling the data of all patients according to the amount of error). It is a question of judgment if the good or acceptable criteria (table 3) are individually good or acceptable and if systolic, diastolic and mean arterial pressures are of equal importance (as presumed for this analysis) for monitoring high-risk surgical patients. Oscillometry showed a high level of individual accuracy and intermittent monitoring was found to be good or acceptable in all 22 patients. With CNAP monitoring a relevant number of individual pressures (26 %) failed to fulfil our liberal definition of "acceptable" (bias ⩽ 10 (12) mm Hg, precision ⩽ 15 mm Hg). The criteria appeared to be too rigorous for systolic pressure (inversely, tonometry particularly failed to identify the peak pressure) but diastolic and mean arterial pressures were also found in the poor category in some patients (table 3). The CNAP method was assessed as a failure in four (18 %) of 22 patients. Adapting the same individual bias criteria to the results of Siegel, Brock-Utne and Brodsky [5], radial artery tonometry was good in six, acceptable in eight and poor in two of their 16 patients, similar to the findings of this study. Most probably, it is not the amount of error *per se* but the unknown direction of pressure changes which makes tonometric monitoring unreliable (e.g. 2 SD of ±27.3 for systolic CNAP indicates a range of 95 % confidence intervals or clinical uncertainty of more than 54 mm Hg) and any subsequent decision for intervention difficult and potentially harmful. Obviously, CNAP monitoring should be interrupted more frequently by oscillometric calibration.

It is not clear why tonometric CNAP specifically failed in four of our 22 patients, indicating the general unpredictability of the method during anaesthesia and surgery. The inter-arm pressure difference, obtained before induction of anaesthesia, showed no correlation with oscillometric and tonometric errors obtained later during the procedure. Nevertheless, it should not be dismissed as irrelevant for dynamic comparison over a longer period. The oscillometric and tonometric errors correlated well on average (fig. 3), but the confidence intervals revealed a considerable degree of disagreement between the two methods. It might be assumed that the combination of factors, such as inter-arm pressure difference and a bidirectional relationship of the oscillometric to invasive, oscillometric to tonometric and tonometric to invasive arterial pressure values, individually influenced the accuracy of each non-invasive method.

Acknowledgements

We thank the Carba-Rüegge Medical Company, Zürich, Switzerland, for providing the Colin instrument.

References

1. Pressman GL, Newgard PM. A transducer for the continuous external measurement of arterial blood pressure. *IEEE Transactions on Biomedical Electronics* 1963; **10**: 73–81.
2. Drzewiecki GM, Melbin J, Noordergraaf A. Arterial tonometry: review and analysis. *Journal of Biomechanics* 1983; **16**: 141–152.
3. Kemmotsu O, Ueda M, Otsuka H, Yamamura T, Winter DC, Eckerle JS. Arterial tonometry for noninvasive, continuous blood pressure monitoring during anesthesia. *Anesthesiology* 1991; 75; 333–340.
4. Kemmotsu O, Ueda M, Otsuka H, Yamamura T, Okamura A, Ishikawa T, Winter DC, Eckerle JS. Blood pressure measurement by arterial tonometry in controlled hypotension. *Anesthesia and Analgesia* 1991; **73**: 54–58.
5. Siegel LC, Brock-Utne JG, Brodsky JB. Comparison of arterial tonometry with radial artery catheter measurements of blood pressure in anesthetized patients. *Anesthesiology* 1994; **81**: 578–584.
6. Kemmotsu O, Ohno M, Tajita K, Sugimoto H, Otsuka H, Morimoto Y, Mayumi T. Noninvasive, continuous blood pressure measurement by arterial tonometry during anesthesia in children. *Anesthesiology* 1994; **81**: 1162–1168.
7. Weiss BM, Hess OM, von Segesser LK, Bernard E, Hegi T, Pasch T. Transducer with a resonance overshoot eliminator: unpredictable accuracy of a damped systolic arterial pressure. *British Journal of Anaesthesia* 1995; 74 (Suppl. 1): A27.
8. Sheiner LB, Beal SL. Some suggestions for measuring predictive performance. *Journal of Pharmacokinetics and Biopharmaceutics* 1981; **9**: 503–512.
9. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1: 307–310.
10. Brunner JMR, Krenis LJ, Kunsman JM, Sherman AP. Comparison of direct and indirect methods of measuring arterial blood pressure (parts I–III). *Medical Instrumentation* 1981; **15**: 11–21, 97–101, 182–188.
11. O'Rourke MF, Avolio A, Kelly RP, Karamanoglu M. Difference between central and upper limb pressure wave forms in man. In: O'Rourke MF, Safar ME, Dzau VJ, eds. *Arterial Vasodilation. Mechanisms and Therapy*. London: Edward Arnold, 1993; 117–133.
12. Borrow KM, Newburger JW. Noninvasive estimation of central aortic pressure using the oscillometric method for analyzing systemic artery pulsatile blood flow: comparative study of indirect systolic, diastolic, and mean brachial artery pressure with simultaneous direct ascending aortic pressure measurements. *American Heart Journal* 1982; **103**: 879–886.
13. Ramsey M. Blood pressure monitoring: automated oscillometric devices. *Journal of Clinical Monitoring* 1991; 7: 56–67.
14. Loubser PG. Comparison of intra-arterial and automated oscillometric blood pressure measurement methods in postoperative hypertensive patients. *Medical Instrumentation* 1986; **20**: 255–259.
15. Gersh BJ. Measurement of intravascular pressures. In: Prys-Roberts C, ed. *The Circulation in Anaesthesia. Applied Physiology and Pharmacology*. Oxford: Blackwell Scientific Publications, 1980; 511–529.
16. Gardner RM. Direct blood pressure measurements—dynamic response requirements. *Anesthesiology* 1981; **54**: 227–236.
17. Hipkins SF, Rutten AJ, Runciman WB. Experimental analysis of catheter–manometer systems in vitro and in vivo. *Anesthesiology* 1989; **71**: 893–906.
18. Frank SM, Norris EJ, Christopherson R, Bettie C. Right- and left-arm blood pressure discrepancies in vascular surgery patients. *Anesthesiology* 1991; **75**: 457–463.
19. Coriat P, Vrillon M, Perel A, Baron JF, Le Bret F, Saada M, Viars P. A comparison of systolic blood pressure variations and echocardiographic estimates of end-diastolic left ventricular size in patients after aortic surgery. *Anesthesia and Analgesia* 1994; **78**: 46–53.
20. Rooke GA, Schwid HA, Shapira Y. The effect of graded hemorrhage and intravascular volume replacement on systolic pressure variation in humans during mechanical and spontaneous ventilation. *Anesthesia and Analgesia* 1995; **80**: 925–932.
21. Urzua J, Sessler DI, Meneses G, Sacco CM, Canessa R, Lema G. Thermoregulatory vasoconstriction increases the differences between femoral and radial artery pressures. *Journal of Clinical Monitoring* 1994; **10**: 229–236.
22. Hynson JM, Sessler DI, Moayeri A, Katz JA. Thermoregulatory and anesthetic-induced alterations in the differences among femoral, radial, and oscillometric blood pressures. *Anesthesiology* 1994; **81**: 1411–1421.
23. Ebstein RH, Bartkowski RR, Huffnagle S. Continuous noninvasive finger blood pressure during controlled hypotension. A comparison with intraarterial pressure. *Anesthesiology* 1991 75: 796–803.
24. Stokes DN, Clutton-Brock T, Patil C, Thompson JM, Hutton P. Comparison of invasive and non-invasive measurement of continuous arterial pressure using the Finapres. *British Journal of Anaesthesia* 1991; **67**: 26–35.
25. Pace NL, East TD. Simultaneous comparison of intraarterial, oscillometric, and Finapres monitoring during anesthesia. *Anesthesia and Analgesia* 1991; **73**: 213–220.
26. Schiller Z, Pasch T. Servo-Plethysmomanometrie zum kontinuierlichen nichtinvasiven Blutdruck-monitoring. *Anaesthesist* 1991; **40**: 105–109.
27. Wilkes MP, Bennett A, Hall P, Lewis M, Clutton-Brock TH. Comparison of invasive and non-invasive measurement of continuous arterial pressure using the Finapres in patients undergoing spinal anaesthesia for lower segment Caesarean section. *British Journal of Anaesthesia* 1994; **73**: 738–743.
28. Young CC, Mark JB, White W, DeBree A, Vender LS, Fleming A. Clinical evaluation of continuous noninvasive blood pressure monitoring: accuracy and tracking capabilities. *Journal of Clinical Monitoring* 1995; **11**: 245–252.
29. Weiss BM, Spahn DR, Keller E, Seifert B, Pasch T. Continuous non-invasive blood pressure monitoring by brachial artery displacement method in high-risk surgical patients. *European Journal of Anaesthesiology* 1995; **12**: 555–563.
30. Association for the Advancement of Medical Instrumentation. *American National Standards for Electronic or Automated Sphygmomanometers*. Arlington, VA: Association for the Advancement of Medical Instrumentation, 1987, updated 1992.
31. O'Brien E, Petrie J, Littler W, De Swiet M, Padfield PL, O'Malley K, Jamieson M, Altman D, Bland M, Atkins N. The British Hypertension Society protocol for the evaluation of automated and semi-automated blood pressure measuring devices with special references to ambulatory systems. *Journal of Hypertension* 1990; **8**: 607–619.

British Journal of Anaesthesia 1996; **76**: 412–414

Haemodilution induces a hypercoagulable state

T. G. RUTTMANN, M. F. M. JAMES AND J. F. VILJOEN

Summary

It has been suggested that haemodilution with saline may increase whole blood coagulation. This study was conducted in two parts. First, we investigated the effect of *in vitro* dilution of blood with saline on whole blood coagulation as measured by the thrombelastogram (TEG). Blood (4 ml) was diluted with 0.9% saline 1 ml and coagulation compared with that of an undiluted control specimen obtained concurrently from the same subject. In the second part, the study was repeated using a modified gelatin colloidal solution (Haemaccel) as the diluent. The *r* time, *k* time and *r*+*k* time were decreased relative to control in both diluent groups. The alpha angles were increased compared with control in both groups while maximum amplitude was unchanged in the Haemaccel diluted group. We conclude that haemodilution *per se* increases the coagulability of whole blood *in vitro*, but that saline haemodilution has a more marked effect on final clot strength. (*Br. J. Anaesth.* 1996; **76**: 412–414)

Key words

Blood, coagulation. Fluids, i.v. Measurement techniques, thrombelastography.

Haemodilution with i.v. fluids decreases the concentration of clotting factors in blood and, intuitively, it would be anticipated that this should induce some degree of impairment of coagulation. There is, however, some evidence that moderate haemodilution with crystalloid solutions may induce a hypercoagulable state [1]. Thrombelastography (TEG) is a technique first developed by Hartert in 1948 [2]. It had little clinical use for many years until it was re-evaluated in 1974 [3]. Subsequently, it was developed further [4] and applied and validated in liver transplantation [5] and cardiac surgery [6].

TEG is essentially a graphic method of displaying the stages in the formation of a whole blood clot (thrombosis) and as such provides a visual pattern of functional clotting status [7]. It has been used to measure coagulation in clinical anaesthesia [8] and we therefore investigated whether or not haemodilution with crystalloid and colloid solutions *in vitro* altered TEG measurements.

Methods

The TEG involves two mechanical parts, a cuvette and a piston. Freshly drawn blood (0.36 ml) is placed in the cuvette which oscillates through 4°45′ at 37 °C. The piston is suspended in the blood sample by a torsion wire which is tranduced to a chart recorder. When no clot exists, the motion of the cuvette does not affect the piston and the chart records a straight line. As strands of fibrin form they attach to the piston and it becomes coupled to the motion of the cuvette, and hence the shearing elasticity of the evolving blood clot is transmitted to the thermal paper.

The TEG pattern is divided into component variables. Reaction time (*r*) is the interval between the start of recording and the time at which the amplitude of the tracing is 2 mm. It reflects the function of the intrinsic clotting pathway. Coagulation time (*r*+*k*) is the time required for the amplitude to reach 20 mm and provides information on not only intrinsic factors but also platelets and fibrinogen, which are also represented by the clot formation rate ($\alpha°$). Maximum amplitude (MA) is the greatest amplitude achieved on the thrombelastogram and is a measure of clot strength and elasticity, again reflecting the properties of platelets and fibrinogen in addition to factor XIII.

The experiment was conducted in two parts. In the first part, blood samples were obtained from 20 healthy, conscious volunteers. Blood was obtained from a free-flowing forearm vein in a 10-ml syringe and separated into two aliquots of 4 ml each in polypropylene plastic tubes. Isotonic saline 1 ml was added to one sample while the other was left undiluted and served as a control. Specimen tubes containing each sample were inverted several times to ensure thorough and similar mixing of blood in each tube. The control samples were inverted in a similar way to those of the diluted group to ensure that, as far a possible, each sample was treated in a similar manner. Specimens from each sample tube (0.360 ml) were then added to the thrombelastograph and simultaneous traces recorded of the normal blood sample and the saline diluted sample. The TEG trace was recorded for 1 h and *r* and *k* times, alpha angle ($\alpha°$), and MA were measured for each sample.

In the second part of the study, the method described above was repeated, except that the test samples were diluted with 1 ml of a modified gelatin colloidal solution (Haemaccel). Again, one sample

---

T. G. RUTTMANN, MB, CHB, FCA(SA), M. F. M. JAMES, MB, CHB, PHD, FRCA, J. F. VILJOEN, MB, CHB, FRCA, Department of Anaesthesia, University of Cape Town Medical School, Observatory, Cape 7925, South Africa. Accepted for publication: September 22, 1995.

Correspondence to T.G.R.

Table 1 TEG values in control and saline diluted samples (mean (SD))

	Control	Saline	P
r (min)	8.3 (2.2)	6.5 (1.7)	0.007
k (min)	3.7 (1.1)	2.2 (0.9)	< 0.001
$r+k$ (min)	12.0 (3.2)	8.8 (2.4)	< 0.001
α (°)	38.7 (9.6)	51.0 (10.1)	< 0.001
MA (mm)	50.7 (6.1)	55.0 (6.4)	0.033

Table 2 TEG values in control and Haemaccel diluted samples (mean (SD))

	Control	Haemaccel	P
r (min)	9.1 (1.6)	7.1 (1.3)	0.001
k (min)	4.3 (1.0)	2.4 (0.8)	< 0.001
$r+k$ (min)	13.4 (2.6)	9.5 (2.2)	< 0.001
α (°)	33.15 (6.4)	49.7 (9.3)	< 0.001
MA (mm)	46.5 (6.4)	47.2 (6.9)	0.08

was used for testing the effect of haemodilution while the other served as a control.

Data from each diluent group were compared with those obtained from the matched controls in each limb of the experiment and any differences noted were analysed for statistical significance using a paired Student's t test.

Results

The results are shown in tables 1 and 2. In the first part of the study there were statistically significant differences between the saline-treated and untreated samples in all variables measured by the thromb-elastograph. There was a highly significant decrease in r and k times, a highly significant increase in the α angle and a more moderate, although still significant, increase in MA.

In the second part of the study, there were statistically significant differences between the Haemaccel-treated and untreated samples for all variables measured by the thrombelastograph, except for MA, which was not affected by dilution with Haemaccel. There was a highly significant decrease in r and k times, and a highly significant increase in the α angle.

Discussion

In 1950, Tocantins, Carroll and Holburn [1] suggested that saline dilution of blood may render it hypercoagulable. This was supported by an *in vivo* study in rats [9]. In 1980, Janvrin, Davies and Greenhalgh [10] demonstrated an increase in the coagulability of whole blood and an increased incidence of postoperative deep vein thrombosis (DVT) in patients treated with i.v. crystalloid during surgery compared with a group who received no i.v. fluid. An *in vivo* study noted that patients receiving crystalloids demostrated an increase in coagulability, as measured by the TEG [11]. This was not attributed directly to the crystalloid infusions. Indeed, some authors have used saline dilution as a control when investigating the effects of other substances on coagulation [12].

We performed an *in vitro* study on human blood using the TEG to compare the dynamic coagulation profile of 20 % haemodilution with either crystalloid or colloid with that of an undiluted control. We have shown that haemodilution with both solutions causes a decrease in r and k times, reflecting increased intrinsic coagulability and platelet and fibrinogen activity. The α angle, reflecting speed of clot formation, was increased significantly in both test groups. Maximum amplitude showed a moderate increase in the saline group, reflecting an increase in clot strength, again indicating increased fibrin and platelet activity, but this effect was not apparent in the colloid diluted group. Mean k time and $r+k$ time for both test groups were shorter than the minimum values quoted by Mallet and Cox [8], although the other measurements were within their quoted ranges. The changes demonstrated in our study represent an increase of 20–40 % in the initiation of coagulation and the speed of clot formation induced by haemodilution, with a lesser effect on the development of clot strength. This implies that moderate haemodilution with either crystalloid or colloid could cause blood to clot more readily, with minimal effects on the strength of the final clot formed. What the effect of greater or lesser degrees of haemodilution might be has not been examined in this study, but Tocantins, Carroll and Holburn [1] suggested that the effect increases with whole blood dilutions of up to 40 % and that the changes in the speed and character of thrombus formation were as a result of haemodilution rather than the properties of saline itself. By repeating the study using a colloid solution as diluent, we have shown similar decreases in r and k times and an increase in α angles, thereby offering further evidence that the documented changes are brought about by dilution rather than by the nature of the actual diluent itself.

Although the intuitive assumption is that haemodilution would increase bleeding tendencies through dilution of coagulation factors, in reality the reserve capacity of the coagulation system under normal conditions is probably so great that dilution is of no relevance unless large volumes are used. Smaller quantities of infused fluids, however, may well activate the coagulation process in several ways, the mechanisms for which would need to be examined if this *in vitro* observation were to be confirmed *in vivo*.

The mechanism by which haemodilution causes this increase in coagulation is far from clear. Tocantins, Carroll and Holburn [1] showed that the nature of the crystalloid diluent was not important, and that all crystalloid solutions produced similar effects; our own unpublished data confirm this impression. They suggested also that haemodilution disturbed the relationship of thrombin and antithrombin resulting in a relative decrease in the concentration of antithrombin, but Monkhouse [9] considered this explanation insufficient to account for his own observations in rats. By performing an *in vitro* study, we have eliminated extraneous factors such as heparinization, stress response, tissue damage and endothelial injury, all of which could affect coagulation in an *in vivo* study. All of the changes we have been able to demonstrate have thus been a direct consequence of the addition of diluent to normal blood.

Our results confirm that the addition of either saline or Haemaccel to a 20% dilution (equivalent to 1000 ml of an i.v. fluid in an average 70-kg person) *in vitro* renders blood hypercoagulable, affecting aspects of the intrinsic coagulation cascade from initial fibrin formation (decreased *r* time), rapidity of fibrin build-up and cross-linkage (decreased *k* time), and speed of clot formation (increased α angle). Final absolute clot strength (MA) was increased only with saline haemodilution and was unchanged with Haemaccel haemodilution. As the TEG measures only the function of the intrinsic pathway, great care was take not to initiate coagulation via the extrinsic pathway.

An in vivo study using the TEG supported by other estimations of coagulation status is necessary to establish coagulation profiles for a range of surgical patients treated with perioperative i.v. fluid solutions.

References

1. Tocantins LM, Carroll RT, Holburn RH. The clot accelerating effect of dilution of blood and plasma. Relation to the mechanism of coagulation of normal and hemophiliac blood. *Blood* 1959; **6**: 720–739.
2. Hartert H. Blutgerinnungstudien mit der Thrombelastographie, einem neuen Untersuchungsverfahren. *Klinische Wochenschrift* 1948; **16**: 257.
3. Howland WS, Schweizer O, Gould P. A comparison of intraoperative measurements of coagulation. *Anesthesia and Analgesia* 1974; **53**: 657–663.
4. Zuckerman L, Cohen E, Vagher JP, Woodward E, Caprini JA. Comparison of thrombelastography with common coagulation tests. *Thrombosis and Haemostatisis* 1981; **46**: 752–756.
5. Kang YG, Martin DJ, Marquez J, Lewis JH, Bontempo FA, Shaw BW, Starzl TE, Winter PM. Intraoperative changes in blood coagulation thrombelastographic monitoring in liver transplantation. *Anesthesia and Analgesia* 1985; **64**: 888–896.
6. Spiess BD, Tuman KJ, McCarthy RJ, De Laria GA, Schillo R, Ivankovich AD. Thrombelastography as an indicator of post-cardiopulmonary bypass coagulopathies. *Journal of Clinical Monitoring* 1987; **3**: 25–30.
7. McNicol PL, Liu G, Harley ID, McCall PR, Przybylowski GM, Bowkett J, Angus PW, Hardy KJ, Jones RM. Patterns of coagulopathy during liver transplantation: Experience with the first 75 cases using thrombelastography. *Anaesthesia and Intensive Care* 1994; **22**: 659–665.
8. Mallet SV, Cox DJ. Thrombelastography. *British Journal of Anaesthesia* 1992; **69**: 307–313.
9. Monkhouse FC. Relationship between antithrombin and thrombin levels in plasma and serum. *American Journal of Physiology* 1959; **197**: 984–988.
10. Janvrin SB, Davies G, Greenhalgh RM. Postoperative deep vein thrombosis caused by intravenous fluids during surgery. *British Journal of Surgery* 1980; **67**: 690–693.
11. Tuman KJ, Spiess BD, McCarthy RJ, Ivankovich AD. Effects of progressive blood loss on coagulation as measured by thrombelastography. *Anesthesia and Analgesia* 1987; **66**: 856–863.
12. Tsunehiro N, Matsumoto I, Kumazawa T, Ikezono E. An experimental study on the effect of plasma expanders on blood coagulability. *Bulletin of the Tokyo Medical and Dental University* 1979; **26**: 25–32.

British Journal of Anaesthesia 1996; **76**: 415–418

Effect of tramadol on depth of anaesthesia

J. F. COETZEE, J. S. MARITZ AND J. C. DU TOIT

Summary

We have studied 51 patients who were anaesthetized with propofol and suxamethonium followed by 0.7% isoflurane and 66% nitrous oxide in oxygen to see if tramadol caused lightening of anaesthesia. A two-channel EEG was recorded and music was played via headphones. Two groups received tramadol 200 and 100 mg i.v. and the third group received saline. Tramadol caused significant, dose-dependent activation of the EEG, evidenced by increased frequencies and decreased amplitudes, but these changes were small and probably unimportant. Derived EEG variables did not approach values known to be associated with near-awakening during isoflurane anaesthesia. No patient moved on skin incision and there were no incidences of free recall. (*Br. J. Anaesth.* 1996; **76**: 415–418)

Key words

Analgesics opioid, tramadol. Anaesthetics volatile, isoflurane. Memory. Anaesthesia, depth.

Tramadol is a relatively new, centrally acting opioid agonist that modifies spinal pain transmission by inhibiting monoamine reuptake. It has been suggested that it is unsuitable for intraoperative use after a 65% incidence of awareness in 20 patients who received tramadol infusions during nitrous oxide anaesthesia supplemented by intermittent administration of low concentrations of enflurane [1]. A recent editorial [2] described the possible risk of awareness associated with intraoperative tramadol administration as a "major drawback" and suggested that "...the risk of intraoperative awareness may represent significant disadvantages for tramadol". The purpose of this study was to determine if single doses of tramadol administered to patients during isoflurane–nitrous oxide anaesthesia resulted in unacceptable lightening of anaesthesia.

Patients and methods

Institutional approval and informed consent were obtained from 51 non-obese, ASA I–II patients, 18–69 yr old, with body weights 42–103 kg. All patients were undergoing orthopaedic and gynaecological surgery. Premedication comprised diazepam 10 mg orally. After attachment of ECG electrodes and preoxygenation, anaesthesia was induced with propofol 1.5–2.0 mg kg^{-1} and the trachea intubated after administration of suxamethonium 1.0 mg kg^{-1}. Patients' lungs were ventilated mechanically, maintaining end-expired carbon dioxide concentration at 4.2–4.8%. Anaesthesia was maintained with 66% nitrous oxide in oxygen and the isoflurane vaporizer was adjusted to maintain an end-expired isoflurane concentration of 0.7% (Siemens Sirecust 734G). No additional doses of neuromuscular blockers were given and recovery from suxamethonium block was confirmed using a nerve stimulator with the stimulating electrodes applied to the skin over the median nerve at the elbow.

The electroencephalogram (EEG) was monitored with a two-channel monitor (Ceregraph, Somchem Ltd, Somerset West, South Africa) using bilateral frontal–ipsilateral mastoid montages via standard silver–silver chloride ECG electrodes. Good electrical contact was ensured by abrading the skin and cleansing with ether. Measured electrode–skin impedances were less than 5 kΩ. The Ceregraph monitor performs power spectral analysis by fast Fourier transform (FFT) on digitized EEG data and stores the derived quantitative descriptors of EEG frequency and amplitude on computer disk: these included 95th percentile power frequency (95%PF), median power frequency (MF) [3] delta ratio (DR) [4], relative delta power (RDP) and root mean square of the EEG signal voltage (RMS).

After maintaining stable end-expired isoflurane concentrations of 0.7% for 20 min, music was played via earphones. Before being placed on the patient, the earphones were applied to an investigator who adjusted the volume control so that the music was heard clearly without experiencing discomfort. The music content was applicable to the patient's cultural background. Patients were allocated randomly to one of three groups (n = 17) who received isotonic saline 4 ml (saline group), tramadol 100 mg (group T100) or tramadol 200 mg (group T200) i.v. The EEG was recorded for another 20 min, after which skin incision was performed. Patient movement within 1 min of incision was recorded. The saline group received morphine 0.2 mg kg^{-1} during operation for postoperative analgesia. A blinded investigator vis-

---

J. F. COETZEE, BSC, MB, CHB, MMED(ANES), DIPDAT, PHD (Department of Anesthesiology); J. S. MARITZ, DSC (University of Witwatersrand, Department of Statistics) University of Stellenbosch/Tygerberg Hospital, PO Box 19063, 7505 Tygerberg, Republic of South Africa. J. C. DU TOIT, MB, CHB, MMED (ANES), Department of Anesthesiology, Tygerberg Hospital, Private bag, 7505 Tygerberg, Republic of South Africa. Accepted for publication: October 10, 1995.

ited the patients on the first postoperative day to enquire about intraoperative recall, including hearing music.

DATA ANALYSIS

Every 4 s the Ceregraph monitor calculated the quantitative EEG descriptors derived from FFT of the previous 8-s epoch and stored these values in an ASCII file on computer disk. During subsequent offline analysis, values for the various EEG descriptors (95%PF, MF, etc.) were tabulated at the following times: before administration of tramadol or saline (0 min), and at 5, 10, 15 and 20 min. Each value was obtained by calculating the mean of 20 readings from the data in the ASCII file. Preliminary analysis of the tabulated data included descriptive statistics (mean, SD, SEM, median) and tests for normality distribution (Komolgorov–Smirnov test). Plots of the mean values of the various EEG descriptors over time were inspected to determine visually if level shifts occurred after administration of tramadol or saline. Distribution-free methods of analysis were used to test if level shifts were significant as follows.

Level shifts within groups

For each EEG descriptor, four successive differences for each subject were calculated: that is the differences in descriptor values between 0–5, 5–10, 10–15 and 15–20 min. The null hypothesis of no level shift stated that the expected values of these differences were zero. A permutation test, that is a distribution-free version of the Hotelling T^2, was performed, as described by Maritz [5]. The end-result of the test is a statistic whose distribution under the null hypothesis is chi-square with 4 degrees of freedom.

Inter-group comparison of level shifts

For each subject, the value of the EEG descriptor at time zero was subtracted from the mean of the values recorded at 5, 10, 15 and 20 min to give a "mean level shift". One-way analysis of variance was performed between groups on these mean level shift values. In addition, a *t* test was performed on the mean level shift of each group to determine if that shift differed significantly from zero.

Comparison of trend profiles between the groups

The trend profiles of the EEG descriptors obtained at 5, 10, 15 and 20 min were considered. In order to determine if the trend profiles over time differed between groups, the null hypothesis states that the expected values of the differences defined above (5–10, 10–15 and 15–20 min) are identical in the three groups. Pairwise comparisons of group profiles were made via a trivariate, two-sample permutation test, that is a distribution-free version of the Hotelling two-sample T^2 was performed that produces a statistic whose distribution under the null hypothesis is chi-square with 3 degrees of freedom. $P = 0.05$ was regarded as indicating statistical significance.

Table 1 Patient data for the three groups (mean (SD or range))

Group	Age (yr)	Weight (kg)
T100	39 (20–61)	67.6 (13.1)
T200	34 (18–55)	62.8 (15.1)
Saline	40 (19–69)	74.3 (16.1)

Results

Patient data are presented in table 1: ages and weights did not differ significantly between groups. No patient moved on skin incision and there were no episodes of intraoperative recall or recollection of music.

EEG CHANGES WITHIN EACH GROUP AFTER TRAMADOL ADMINISTRATION

There were no significant EEG changes in the saline group (table 2). In contrast, both tramadol groups showed significantly increased EEG frequencies and decreased amplitudes within 5 min of drug administration and these appearances were maintained throughout the measuring period. These changes were expressed by increased MF, DR and 95%PF and decreased RMS and RDP.

INTER-GROUP COMPARISON OF MEAN EEG CHANGES AFTER TRAMADOL ADMINISTRATION

After tramadol administration, mean EEG changes in group T200 were significantly different from those of the saline group but did not differ from those of group T100. In group T100, mean level shifts of all EEG descriptors did not differ significantly from those of the saline and T200 groups.

INTER-GROUP COMPARISON OF TREND PROFILES AFTER TRAMADOL ADMINISTRATION

The post-injection trend profiles of all EEG descriptors were similar in the saline and T200 groups. The 95% PF and left RMS in group T100 differed significantly from those of the two other groups.

Discussion

Administration of tramadol during stable, light nitrous oxide isoflurane anaesthesia resulted in increased EEG frequencies (increased MF, DR and 95%PF, and decreased RDP) and decreased EEG amplitude (decreased RMS). These changes were maintained throughout the 20-min measurement period. Lightening of anaesthesia usually leads to increasing EEG frequencies of lower amplitude and two of the descriptors used in this study have been shown to indicate near-awakening during isoflurane–nitrous oxide anaesthesia [3, 4]. Schwilden and Stoeckel [3] concluded that there was an increased probability of patient awareness if the MF exceeded 5–6 Hz. Long and colleagues [4] found that near-

Table 2 Mean (SD) values for the various univariate EEG descriptors of the three groups obtained at different times. Stage 0 = Before injection, stages 5, 10, 15 and 20 = 5, 10, 15 and 20 min after injection, respectively. There were 17 subjects in each group. Results from the right side only are presented, because left-sided values were similar. 95% PF = 95th percentile power frequency, MF = median power frequency, RDP = relative delta power, DR = delta ratio, RMS = root mean square of the EEG signal voltage

	Group T100					Group T200					Saline group				
	Stage					Stage					Stage				
	0	5	10	15	20	0	5	10	15	20	0	5	10	15	20
95% PF (Hz)	9.7 (0.5)	11.1 (0.5)	10.1 (0.7)	10.1 (0.6)	9.9 (1.7)	9.8 (0.6)	13.1 (0.4)	12.7 (1.0)	12.9 (1.0)	12.7 (1.0)	9.1 (0.7)	9.2 (0.6)	9.3 (0.7)	9.5 (0.8)	9.6 (0.6)
MF (Hz)	1.0 (0.1)	1.6 (0.2)	1.6 (0.2)	1.5 (0.2)	1.5 (0.4)	1.4 (0.3)	2.5 (0.5)	2.3 (0.4)	2.3 (0.5)	2.2 (0.4)	1.1 (0.3)	1.1 (0.2)	1.1 (0.2)	1.2 (0.2)	1.1 (0.1)
RDP	0.78 (0.03)	0.73 (0.04)	0.75 (0.03)	0.75 (0.03)	0.73 (0.04)	0.76 (0.03)	0.68 (0.03)	0.67 (0.03)	0.66 (0.03)	0.66 (0.03)	0.79 (0.03)	0.80 (0.03)	0.80 (0.03)	0.79 (0.03)	0.79 (0.03)
DR	1.22 (0.03)	1.30 (0.06)	1.29 (0.05)	1.29 (0.05)	1.29 (0.05)	1.29 (0.07)	1.51 (0.13)	1.46 (0.11)	1.50 (0.13)	1.47 (0.11)	1.22 (0.06)	1.21 (0.05)	1.22 (0.05)	1.23 (0.05)	1.21 (0.04)
RMS (μV)	66 (9)	59 (8)	61 (9)	60 (8)	60 (8)	69 (10)	53 (7)	53 (8)	55 (8)	57 (8)	47 (8)	48 (8)	46 (8)	47 (8)	45 (8)

awakening occurred at DR values of approximately 2. The EEG changes caused by administration of tramadol in our patients, although statistically significant, were subtle and small, the values not approaching those that have been found to occur during near-awakening. The EEG changes may therefore be clinically insignificant.

It is possible that the effects of tramadol may be dose-dependent, as indicated by the tendency towards different post-injection profiles in group T100 (95%PF and RMS) and by the observation that the mean level shifts of group T100 were not different from the two other groups, whereas the mean level shift in group T200 differed significantly from that of the saline group.

All patients in the study remained sufficiently anaesthetized so that they did not move during skin incision and the initial stages of the operative procedures. Furthermore, there was no evidence of intraoperative conscious recall, either spontaneously or on enquiry. It may be argued that inability to recall music and lack of movement on surgical stimulation are insensitive indicators of awareness during anaesthesia. Lehmann, Horrichs and Hoeckle [1] found free recall of conscious awareness by playing music to their patients and similarly we endeavoured to seek *conscious* awareness without amnesia in our patients. This should be distinguished from the more subtle manifestations of wakefulness during anaesthesia, namely conscious awareness with amnesia and subconscious awareness with amnesia [6], which would have required detection by different methods, such as the isolated forearm technique [7, 8] or cued word lists [9].

Movement on skin incision is not concerned directly with consciousness but is a generally accepted sign of inadequate anaesthesia. If the groups who had received tramadol had demonstrated a greater incidence of movement on skin incision than the saline group, this may have suggested that tramadol antagonized anaesthesia. The absence of this sign was also an important monitor of the ethics of the study, because a high incidence of movement on skin incision in the tramadol groups may have necessitated termination of the study.

The three methods of monitoring depth of anaesthesia, that is minor EEG changes, lack of movement on skin incision and absence of spontaneous conscious recall, suggest that tramadol, in doses up to 200 mg i.v., given to adults during stable, light isoflurane–nitrous oxide anaesthesia, did not lead to clinically significant lightening of anaesthesia in this study.

Acknowledgement

The work was supported by a grant from Grunenthal GmbH, Stolberg, Germany.

References

1. Lehmann KA, Horrichs G, Hoeckle W. Tramadol as an intraoperative analgesic. A randomized double blind study with placebo. *Anaesthesist* 1985; 34: 11–19.
2. Eggers KA, Power I. Tramadol. *British Journal of Anaesthesia* 1995; 74: 247–248.

3. Schwilden H, Stoeckel H. Quantitative EEG analysis during anaesthesia with isoflurane in nitrous oxide at 1.3 and 1.5 MAC. *British Journal of Anaesthesia* 1987; **59**: 738–745.
4. Long CW, Shah NK, Loughlin C, Spydell J, Bedford RF. A comparison of EEG determinants of near-awakening from isoflurane and fentanyl anesthesia. Spectral edge, median power frequency, and delta ratio. *Anesthesia and Analgesia* 1989; **69**: 169–173.
5. Maritz JS. Models and the use of signed rank tests. *Statistics in Medicine* 1985; **4**: 145–153.
6. Jones JG, Konieczko K. Hearing and memory in anaesthetized patients. *British Medical Journal* 1986; **292**: 1291–1293.
7. Tunstall ME. Detecting wakefulness during general anaesthesia for caesarean section. *British Medical Journal* 1977; **1**: 1321.
8. Tunstall ME. The reduction of amnesic wakefulness during caesarean section. *Anaesthesia* 1979; **34**: 316–319.
9. Millar K. Recall, recognition and implicit memory for intra-anaesthetic events. *Baillière's Clinical Anaesthesiology* 1989; **3**: 487–510.

British Journal of Anaesthesia 1996; **76**: 419–427

LABORATORY INVESTIGATIONS

Effects and interactions of myocardial ischaemia and alterations in circulating blood volume on canine left ventricular diastolic function

S. DALMAS, S. C. U. MARSCH, D. M. PHILBIN, D. J. GAVAGHAN, W. A. RYDER AND P. FOËX

Summary

We have determined the effects of alterations in preload on ischaemia-induced diastolic dysfunction in anaesthetized beagles instrumented to measure left ventricular pressure and regional dimensions. Low-flow regional ischaemia decreased peak lengthening rates in ischaemic (mean −26 (SEM 6) mm s^{-1}, $P < 0.01$) and non-ischaemic (−8.6 (3.4) mm s^{-1}, $P < 0.05$) myocardium. Peak lengthening rates and the time constant of isovolumic relaxation (τ) were not affected by alterations in preload. Absolute values of τ failed to distinguish between ischaemia and control. The ischaemia-induced decrease in peak negative dP/dt was preload dependent and caused mainly by a concomitant decrease in peak left ventricular pressure. We conclude that indices derived from segmental lengthening are sensitive to ischaemia and insensitive to preload, in contrast with indices derived from left ventricular pressure. It remains to be determined if monitoring of early segmental lengthening will improve detection and assessment of perioperative myocardial ischaemia. (*Br. J. Anaesth.* 1996; **76**: 419–427)

Key words

Heart, ischaemia. Heart, myocardial function. Heart, ventricles. Blood, volume. Dog.

Myocardial ischaemia has profound effects on both systolic and diastolic cardiac performance. There is, however, clinical and experimental evidence that diastolic function is particularly sensitive to myocardial ischaemia. Dodek, Kassebaum and Bristow reported repeated episodes of pulmonary oedema in patients with a normal heart size [1]. Moreover, despite the absence of systolic dysfunction, diastolic dysfunction may occur in a high proportion of patients with coronary artery disease, both at rest and during pacing-induced ischaemia [2, 3]. In experimental models of myocardial ischaemia, diastolic dysfunction precedes contractile dysfunction [4] or may even be the predominant, if not only, sequel of ischaemia [5].

Given the impact of myocardial ischaemia on cardiac morbidity and mortality [6], early detection and rigorous treatment of ischaemic episodes might lead to improvement in perioperative outcome. Recent advances in technology allow non-invasive assessment of diastolic function using echocardiography (segmental re-extension), pulsed wave Doppler echocardiography (filling pattern), or both. However, even mild alterations in preload (change in end-diastolic pressure ±4–5 mm Hg) were reported to mimic or mask diastolic dysfunction as derived from the mitral inflow velocity profile [7, 8]. As rapid and substantial changes in preload cannot be excluded in the perioperative period, preload-induced modifications have to be taken into account in order to interpret indices of diastolic function. It is currently not known if and how alterations in preload affect regional segmental lengthening or interact with ischaemia-induced alterations in the pattern of left ventricular relaxation and lengthening.

The aim of the present investigation was to determine the effects and interactions of alterations in circulating blood volume on global and regional indices of left ventricular diastolic function in the absence and presence of myocardial ischaemia.

Materials and methods

EXPERIMENTAL PREPARATION

The study conformed to the United Kingdom Animals Act (Scientific Procedures, 1986, Home Office licence No. PPL 30/00887). Nine beagles of both sexes (mean weight 14.4 (SEM 1.2) kg) were premedicated with morphine 1.0 mg kg^{-1} i.m. Anaesthesia was induced with sodium thiopentone 10 mg kg^{-1} i.v. and maintained with 1.0–1.5% halothane and nitrous oxide in oxygen ($FI_{O_2} = 0.4$).

SERGE DALMAS*, MD, STEPHAN C. U. MARSCH†, MD, DPHIL, DAVID J. GAVAGHAN, DPHIL, WILLIAM A. RYDER, PIERRE FOËX, MD, DPHIL, Nuffield Department of Anaesthetics, Radcliffe Infirmary, Oxford, UK. DANIEL M. PHILBIN, MD, Harvard Medical School, Massachusetts General Hospital, Boston, USA. Accepted for publication: October 10, 1995.

Present addresses:

* Hôpital Claude Huriez, Place de Verdun, 59037 Lille Cédex, France.

† Departement Anästhesie, Kantonsspital, 4031 Basel, Switzerland.

Correspondence to P.F.

Inspiratory and end-tidal gas concentrations were measured continuously (gas analyser M1025A, Hewlett-Packard, Bracknell, UK) and mechanical ventilation was adjusted to maintain the end-tidal carbon dioxide concentration at 4.5–5.5%. Mid-oesophageal temperature was maintained at 36–37 °C using a Servo-controlled heating element incorporated into the operating table. Ringer's lactate 5 ml kg^{-1} h^{-1} was infused continuously through an i.v. cannula inserted in the left hind leg. A left thoracotomy was performed, the fifth and sixth ribs excised, and the heart isolated and suspended in a pericardial cradle.

INSTRUMENTATION

Instrumentation included limb lead II of the electrocardiogram (subcutaneous electrodes); an 8-French gauge fluid-filled cannula in the left common carotid artery for withdrawal of blood; a 7-French gauge pulmonary artery catheter (Swan–Ganz, American Edwards Laboratories, Anasco, Puerto Rico) inserted into the pulmonary artery via the left jugular vein; a micromanometer-tipped 8-French gauge catheter (Millar, Houston, TX, USA) inserted into the aortic arch via the right femoral artery for measurement of systemic pressures; a second micromanometer-tipped 8-French gauge catheter in the left ventricle (inserted via a stab wound in the apical dimple) for measurement of ventricular pressures; Doppler flow probes (Triton, San Diego, CA, USA) placed around the proximal ascending aorta and the left anterior descending coronary artery (LAD) distal to its first diagonal branch; a snare positioned distal to the flow probe on the LAD and attached to a micrometer controlled occluder; and two pairs of piezoelectric crystals (5 MHz, 2 mm in diameter, Triton Technologies, San Diego, CA, USA) implanted approximately 1 cm apart in a circumferential plane via small epicardial stab wounds in the subendocardium of a near apical (ischaemic area, supplied by the LAD) and a basal area (non-ischaemic area, supplied by the left circumflex coronary artery) for ultrasonic measurement of segmental length.

After completion of surgery and instrumentation, arterial blood-gas analysis was performed, and ventilation adjusted if necessary. Halothane was discontinued, a bolus dose of fentanyl 100 μg kg^{-1} administered, and a continuous infusion of fentanyl 2 μg kg^{-1} min^{-1} commenced and maintained throughout the study. After a stabilization period of 1 h, 200 ml of arterial blood (four aliquots with 50 ml each) was obtained and kept at body temperature in a heated water bath while 200 ml of Dextran (5%, average molecular weight 70000) was infused into the femoral vein. A period of 30 min was then allowed for the haemodynamic state to stabilize before the circulating blood volume was increased stepwise: after recording baseline haemodynamic variables, 50 ml of blood was infused in the femoral vein over 30 s and further haemodynamic variables were recorded 1 min after completion of the infusion. Infusion of the following aliquot was started 3 min after completion of the previous infusion. This was repeated three times (total volume infused 200 ml). The 200 ml of blood was then withdrawn over a period of 15 min. After a stabilization period of 10 min, the snare around the LAD was tightened until the onset of obvious systolic lengthening, as assessed by the apical circumferential length–ventricular pressure loop (tilt of the loop to the right) which was displayed continuously on an oscilloscope. After completion of baseline recordings 10 min after the onset of ischaemia, the circulating blood volume was increased in a manner identical to that described for the control stage.

DATA COLLECTION AND ANALYSIS

ECG, pressure (aortic, left ventricular, airway), flow (aortic, coronary) and myocardial segment lengths signals were converted using an analogue-digital converter (AT-MIO-16, National Instruments Corporation, Austin, TX, USA) and displayed continuously on the screen of an IBM AT personal computer using the real-time mode software designed in this department. After every volume modification, data were recorded at a sampling frequency of 500 Hz during a period of three respiratory cycles and stored on the hard disk. Cardiac output was measured in triplicate by thermodilution (COM-2 Baxter, Santa Ana, USA) before the start of volume modification at each stage.

At the end of the experiment, the animals were killed with an overdose of halothane. A fine catheter was inserted into the LAD and 5 ml of Evans blue dye injected. In all animals necropsy confirmed the subendocardial placement of the crystals within or outside the blue stained region.

Data analysis was performed on an IBM AT personal computer using the play-back mode of the above-mentioned software. To minimize the respiratory effects on haemodynamic variables, end-expiratory data were used for analysis. The first derivative of left ventricular pressure (dP/dt) was obtained by electronic differentiation. End-diastole was defined as the first upward (positive) deflection of the left ventricular dP/dt signal. End-systole was defined as the first return to zero of the aortic flow signal.

REGIONAL WALL MOTION

Length measures were normalized to an initial end-diastolic length of 10 mm. The following variables were used to quantify regional wall motion: end-diastolic length (EDL); end-systolic length (ESL); minimum diastolic length (L_{min}); and maximum length during systole (L_{max}). Total shortening was defined as $EDL - L_{min}$ (mm). Systolic shortening was defined as $EDL - ESL$ and expressed as a percentage of total shortening. Post-systolic shortening was defined as $ESL - L_{min}$ and expressed as a percentage of total shortening. Thus systolic and post-systolic shortening together = 100%. Systolic lengthening was defined as $L_{max} - EDL$ and expressed as a percentage of EDL.

TIME CONSTANT OF ISOVOLUMIC RELAXATION

The time constant of isovolumic relaxation (τ) was obtained by the method described originally by Weiss, Frederiksen and Weisfeldt [9]: the slope of the natural logarithm of left ventricular pressure (P) *vs* time (t) relation (from peak $-\mathrm{d}P/\mathrm{d}t$ to the ventricular pressure that exceeds end-diastolic pressure by 10 mm Hg) was obtained by a least squares linear regression and τ was defined as the negative inverse of that slope:

$$\ln P = At + c$$
$$\tau = 1/-A$$

where A = slope and c = intercept of the $\ln P$ *vs* t relation.

The rationale for the use of a method which assumes an asymptotical pressure–stress decay to zero rather than an asymptotical decay to an unknown baseline pressure–stress was that values yielded by the former approach are much closer to the "true" time constant of isovolumic relaxation obtained by preventing filling and thus allowing the ventricle to relax completely [10].

LENGTHENING

The base value of lengthening was defined as L_{min} and the interval between the preceding R wave of the ECG and L_{min} was defined as the R–L_{min} interval. The peak lengthening rate (PLR) was obtained by electronic differentiation and the interval between the preceding R wave of the ECG and PLR was defined as the R–PLR interval. Relaxation time (RT) was defined as the interval between peak negative $\mathrm{d}P/\mathrm{d}t$ and the time when lengthening rate had decreased to 50% of PLR [11]. The end of the rapid lengthening phase was defined as the time when the lengthening rate had decreased to less than 2 mm s^{-1} (normalized units and hence equal to a lengthening rate of 0.2 (end-diastolic length) per second). The segmental length at this time was termed L_{ms} (length at minimum speed). Thus L_{ms} divides segmental re-extension into a rapid and slow portion [12]. The fraction of lengthening occurring during the rapid lengthening period (RL%) was expressed as a percentage of total lengthening:

$$\mathrm{RL\%} = [(L_{ms} - L_{min})/(\mathrm{EDL} - L_{min})] \times 100$$

STATISTICS

All values are expressed as mean (SEM). Data were analysed on an IBM AT personal computer using SPSS, a commercially available statistical analysis program (SPSS for Windows, Release 5, SPSS Inc, Chicago, IL, USA). $P < 0.05$ was considered to represent statistical significance. Means of the two different stages were compared by a paired Student's *t* test. Combined effects of volume loading and the experimental interventions (control, ischaemia) on global and regional haemodynamics were assessed using GLIM (generalized linear interactive modelling, version 3.77 update 2, The Royal Statistical Society, London, UK). Interactive modelling was performed by forward stepwise multiple linear regression ($P < 0.05$ for inclusion or exclusion of a variable as obtained by F-test) for the following equation:

$$\text{Variable} = \text{constant} + V \times (\text{infused volume in ml}) + S_i(\text{ischaemia}) + I_i(\text{interaction volume/ischaemia})$$

where V, S, and I = maximum likelihood variable estimates. The constant and the term S are expressed in the units of the variable concerned, while the terms V and I are expressed in units of the variable concerned per millilitre volume infused. A significant term for V indicates a correlation between volume loading and dependent variable; a significant term for S indicates a parallel shift of the regression line compared with baseline; a significant term for I indicates a difference in slope. For all variables tested, models assuming a liner relationship between dependent variable and volume yielded a better fit (as indicated by residual sum of squares) than models assuming a log-linear relationship.

Results

GLOBAL FUNCTION

Infusion of 200 ml of blood increased left ventricular end-diastolic pressure from 6.7 (0.6) to 11.3 (0.9) mm Hg during control experiments and from 7.7 (0.8) to 13.2 (1.6) mm Hg during ischaemia. The combined effects of myocardial ischaemia and volume loading on global cardiac function are shown in table 1.

EFFECTS OF MYOCARDIAL ISCHAEMIA ON REGIONAL WALL MOTION

During ischaemia, coronary blood flow velocity in the LAD was reduced to 16 (4)% of control. In the ischaemic area (LAD supply) this resulted in a marked reduction in total shortening; systolic shortening was replaced almost completely by haemodynamically ineffective post-systolic shortening (table 2). Myocardial ischaemia did not affect regional wall motion in the remote non-ischaemic area.

PEAK NEGATIVE $\mathrm{d}P/\mathrm{d}t$

Combined effects of ischaemia and alterations in circulating blood volume on peak negative $\mathrm{d}P/\mathrm{d}t$ ($-\mathrm{d}P/\mathrm{d}t$) are shown in figure 1. Note the significant and independent effects of both volume loading and myocardial ischaemia. Figure 2 demonstrates that a highly significant correlation ($r > 0.95$, $P < 0.001$) between peak negative $\mathrm{d}P/\mathrm{d}t$ and peak left ventricular pressure (LVP) was preserved during myocardial ischaemia. Assessing the combined effects of ischaemia, peak LVP and alterations in circulating blood volume on $-\mathrm{d}P/\mathrm{d}t$, general linear interactive modelling yielded the following variable estimates (SEM):

$$-\mathrm{d}P/\mathrm{d}t\,(\text{mm Hg s}^{-1}) = -105\,(321) + [24\,(2) \times \text{LVP}] - [1.5\,(0.7) \times \text{volume}] - [267\,(102)\text{ if ischaemic}].$$

Table 1 Effect of volume loading on global haemodynamics (mean (SEM)) during control and myocardial ischaemia. For the sake of clarity only three of the five stages of the loading procedure are shown. Variable estimates (SEM) were obtained using general linear interactive modelling (see text). None of the interactive terms (not displayed) proved to be significant at the 0.05 level for any variable. $*P < 0.05$, $**P < 0.01$. Example: the model predicts systolic arterial pressure at the 200 ml level during ischaemia as follows: 151 mm Hg + 200 (9×10^{-2}) mm Hg − 17 mm Hg = 152 mm Hg

		Volume infused (ml)			Variable estimates		
		0	100	200	Constant	Volume ($\times 10^{-2}$)	Ischaemia
Heart rate (beat min^{-1})	Control	121 (8)	118 (8)	123 (6)	125 (3)	0	0
	Ischaemia	132 (12)	129 (9)	127 (8)			
Systolic arterial pressure (mm Hg)	Control	146 (8)	161 (9)	168 (9)	151 (5)	9 (4)*	−17 (5)**
	Ischaemia	134 (10)	143 (8)	150 (7)			
Diastolic arterial pressure (mm Hg)	Control	92 (5)	106 (6)	111 (6)	97 (4)	7 (3)**	0
	Ischaemia	93 (8)	100 (7)	105 (6)			
LV end-diastolic pressure (mm Hg)	Control	6.7 (0.6)	8.7 (0.6)	11.3 (0.9)	7.0 (0.6)	2.3 (0.5)**	1.4 (0.6)*
	Ischaemia	7.7 (0.8)	10.5 (1.2)	13.2 (1.6)			
Peak positive d*P*/d*t* (mm Hg s^{-1})	Control	3289 (396)	3274 (372)	3399 (353)	3280 (132)	0	−638 (187)**
	Ischaemia	2527 (245)	2663 (217)	2778 (252)			

Peak LVP was the single most important predictor ($F_{(1,88)} = 164$) and accounted for 66% of the overall variance (volume 4%, ischaemia 2%, residual variance 29%).

TIME CONSTANT OF ISOVOLUMIC RELAXATION

The time constant of isovolumic relaxation (τ) increased consistently during ischaemia which resulted in a significant difference between control and ischaemia when assessed by paired comparison. However, when the combined effects of ischaemia and alterations in circulating blood volume on τ were assessed by general linear interactive modelling, the term "ischaemia" failed to reach statistical significance. Thus absolute values for τ could not distinguish between control and ischaemia. Only when values for τ were normalized to an initial value of 100% did a significant effect of myocardial ischaemia become apparent (variable estimate + 6.5 (1.5)%, $P \leqslant 0.01$). Alterations in circulating blood volume had no significant effect on τ (for both absolute values and percentage changes) during both baseline and ischaemia (fig. 3).

REGIONAL LENGTHENING

In the control stage, there was a significant inter-regional difference in peak lengthening rate (apex 68 (11) mm s^{-1}; base 45 (5) mm s^{-1}; $P < 0.05$), relaxation time (apex 123 (6) ms; base 88 (4) ms; $P < 0.05$) and R–PLR interval (apex 325 (14) ms; base 290 (11) ms; $P < 0.05$).

The combined effects of ischaemia and volume loading on regional indices in ischaemic and non-ischaemic myocardium are shown in tables 3 and 4. Note that despite a significant increase in the $R–L_{mm}$ interval in the ischaemic area, the interval between R wave and peak lengthening rate (R–PLR) remained unchanged. Likewise, the decrease in $R–L_{mm}$ of the remote non-ischaemic area was accompanied by an unchanged R–PLR interval. Myocardial ischaemia was associated with a decrease in PLR in both ischaemic and remote non-ischaemic myocardium and in neither area did volume loading modify PLR during the control and ischaemic stages.

Discussion

Myocardial ischaemia affected the lengthening pattern in both ischaemic and remote non-ischaemic myocardium: in ischaemic myocardium the beginning of the lengthening period was delayed and PLR was reduced markedly while in remote non-ischaemic myocardium, lengthening started earlier and there was a moderate decrease in PLR. These changes were not modified by alterations in circulating blood volume. Moreover, alterations in circulating blood volume did not affect the time constant of isovolumic relaxation, both in the presence or absence of myocardial ischaemia. A highly significant correlation between peak negative d*P*/d*t* and peak LVP was preserved during the ischaemic period and peak LVP was the most important predictor of peak negative d*P*/d*t*.

GLOBAL DIASTOLIC FUNCTION

A decrease in peak negative d*P*/d*t* and an increase in both time constant of isovolumic relaxation (τ) and end-diastolic pressure are well established features of myocardial ischaemia both in humans and in a variety of experimental models [3–5, 13, 14].

PEAK NEGATIVE d*P*/d*t* (−d*P*/d*t*)

In the absence of myocardial ischaemia, −d*P*/d*t* is influenced by left ventricular contractility, end-systolic volume and mean aortic pressure [15, 16]. Consistent with the present findings, Gaasch and colleagues observed an increase in −d*P*/d*t* when an increase in preload, caused by volume expansion, was accompanied by an increase in afterload [17]. In contrast, an isolated increase in preload (increase in afterload prevented by aortic unloading) resulted in unchanged values for −d*P*/d*t*. Bahler and Martin observed a decrease in −d*P*/d*t*, associated with a decrease in peak systolic LVP, following a decrease

Table 2 Effect of volume loading on regional wall motion in ischaemic myocardium (mean (SEM)) during control and myocardial ischaemia. For the sake of clarity only three of the five stages of the loading procedure are shown. Systolic shortening and post-systolic shortening are expressed as a percentage of total shortening (TS) and add up to 100%. Variable estimates (SEM) were obtained using general linear interactive modelling (see text). The interactive term ($V \times I$) indicates an effect of volume loading during the ischaemic state. $^{*}P < 0.05$, $^{**}P < 0.01$

		Volume infused (ml)			Variable estimates			
		0	100	200	Constant	Volume ($\times 10^{-2}$)	Ischaemia	Interaction ($V \times I$)
Systolic lengthening (%)	Control	0	0	0	0 (0.3)	0	14.1 (4)**	−3.2 (1)*
	Ischaemia	14.7 (1.7)	10.9 (1.9)	7.9 (1.3)				
Total shortening (mm)	Control	3.06 (0.36)	3.02 (0.34)	2.99 (0.25)	3.03 (0.13)	0	−1.540 (45)**	0
	Ischaemia	1.34 (0.24)	1.48 (0.23)	1.61 (0.5)				
Systolic shortening (% of TS)	Control	98 (2)	97 (2)	98 (2)	97 (1)	0	−94 (5)	0
	Ischaemia	3 (1)	3 (1)	3 (1)				
Post-systolic shortening (% of TS)	Control	2 (2)	3 (2)	2 (2)	2 (1)	0	95 (6)**	0
	Ischaemia	97 (1)	97 (1)	97 (1)				

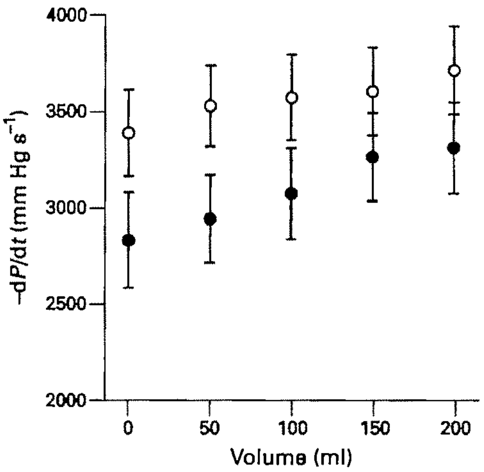


Figure 1 Combined effects of myocardial ischaemia and alterations in circulating blood volume on peak negative dP/dt ($-dP/dt$) during control (○) and myocardial ischaemia (●) (mean, SEM). Both ischaemia and volume loading had a significant and independent effect on $-dP/dt$. Variable estimates as obtained from general linear interactive modelling (GLIM) predicted: dP/dt (mm Hg s^{-1}) as 3452 (132) +(2.0 (0.9) × volume in ml) − (612 (132) if ischaemic) (see text for further explanation).

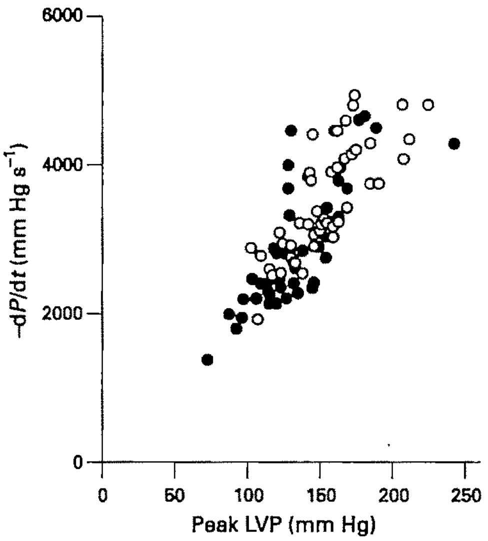


Figure 2 Correlation between peak negative dP/dt ($-dP/dt$) and peak left ventricular pressure (LVP) during control (○) and regional myocardial ischaemia (●).

in preload induced by caval occlusion [11]. In addition to confirming their finding of a highly significant correlation between $-dP/dt$ and peak LVP in normally perfused myocardium, our study has demonstrated that this correlation was well preserved during myocardial ischaemia. Using interactive statistical modelling we demonstrated that peak LVP was the most important predictor of $-dP/dt$. Thus the decrease in peak negative dP/dt, associated with myocardial ischaemia, appears to reflect mainly an ischaemia-induced decrease in developed pressure rather than direct impairment of early relaxation.

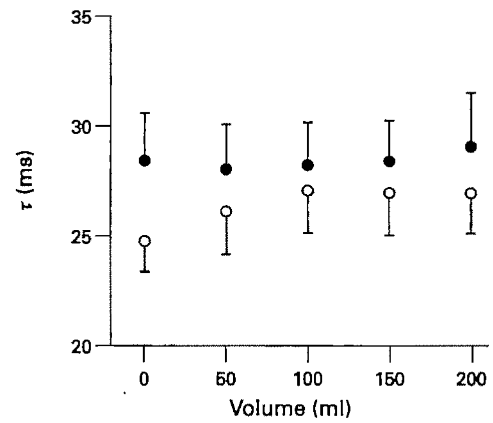


Figure 3 Combined effects of myocardial ischaemia and alterations in circulating blood volume on the time constant of isovolumic relaxation (τ) (mean, SEM). Although τ increased consistently during myocardial ischaemia, absolute values did not distinguish between control (○) and ischaemia (●), as indicated by the overlapping error bars.

TIME CONSTANT OF ISOVOLUMIC RELAXATION

Although a consistent increase in the time constant of isovolumic relaxation (τ) occurred, absolute values for τ failed to distinguish between control and myocardial ischaemia. Only when values for τ were normalized to an initial value of 100% could generalized linear interactive modelling detect a significant effect of myocardial ischaemia. These statistical findings may be explained by the comparatively small number of animals in our study and the large inter-individual variance of τ. A similar inter-individual variance of τ was found in a previous clinical investigation which failed to demonstrate a significant difference in τ between patients with and without coronary artery disease [8]. Although load-dependence of τ has been reported repeatedly [17–20] there is controversy as to whether alterations in preload affect τ: Raff and Glantz found that volume loading increased τ and that the end-diastolic pressure was an independent predictor of τ, as assessed by multiple linear regression analysis [19]. In contrast, Karliner and colleagues reported that volume loading had no effect on τ [18]. Moreover, Bahler and Martin found that τ remained unchanged after a reduction in preload caused by caval occlusion [11]. In addition, Gaasch and colleagues [17, 20] demonstrated that volume loading did not affect τ provided that left ventricular systolic pressure

Table 3 Effect of volume loading on segmental lengthening in ischaemic myocardium (mean (SEM)) during control and myocardial ischaemia. For the sake of clarity only three of the five stages of the loading procedure are shown. Variable estimates (SEM) were obtained using general linear interactive modelling (see text). None of the interactive terms (not displayed) proved to be significant at the 0.05 level for any variable. R–PLR = Interval between preceding R wave of the ECG and the peak lengthening rate, $R\text{–}L_{min}$ = interval between the preceding R wave of the ECG and the minimum segment length, RL = fraction of total lengthening during the rapid lengthening phase. $^{**}P < 0.01$

		Volume infused (ml)			Variable estimates		
		0	100	200	Constant	Volume ($\times 10^{-2}$)	Ischaemia
Peak lengthening rate (mm s^{-1})	Control	68 (11)	71 (10)	73 (11)	73 (4)	0	−26 (6)**
	Ischaemia	44 (9)	49 (10)	51 (13)			
R–PLR interval (ms)	Control	325 (14)	333 (14)	336 (14)	329 (6)	0	0
	Ischaemia	321 (17)	330 (13)	332 (13)			
$R\text{–}L_{min}$ interval (ms)	Control	222 (16)	250 (18)	266 (14)	245 (7)	0	50 (10)**
	Ischaemia	290 (18)	297 (17)	301 (16)			
Relaxation time (ms)	Control	123 (6)	122 (6)	123 (6)	120 (2)	0	0
	Ischaemia	122 (5)	118 (5)	116 (6)			
RL (%)	Control	84 (4)	88 (5)	87 (4)	85 (3)	0	−12 (5)
	Ischaemia	69 (7)	68 (3)	73 (4)			

Table 4 Effect of volume loading on segmental lengthening in non-ischaemic myocardium (mean (SEM)) during control and myocardial ischaemia. For the sake of clarity only three of the five stages of the loading procedure are shown. Variable estimates (SEM) were obtained using general linear interactive modelling (see text). None of the interactive terms (not displayed) proved to be significant at the 0.05 level for any variable. R–PLR = Interval between preceding R wave of the ECG and the peak lengthening rate, $R\text{–}L_{mm}$ = interval between the preceding R wave of the ECG and the minimum segment length, RL = fraction of total lengthening occurring during the rapid lengthening phase. $^{*}P < 0.05$, $^{**}P < 0.01$

		Volume infused (ml)			Variable estimates		
		0	100	200	Constant	Volume ($\times 10^{-2}$)	Ischaemia
Peak lengthening rate (mm s^{-1})	Control	45 (5)	45 (7)	45 (7)	44 (2)	0	−9 (7)*
	Ischaemia	31 (5)	35 (6)	31 (5)			
R–PLR interval (ms)	Control	290 (11)	296 (11)	299 (10)	281 (5)	0	0
	Ischaemia	275 (18)	285 (15)	276 (17)			
$R\text{–}L_{min}$ interval (ms)	Control	237 (10)	244 (5)	243 (5)	241 (4)	0	−32 (6)**
	Ischaemia	198 (13)	211 (8)	214 (7)			
Relaxation time (ms)	Control	88 (4)	85 (4)	88 (5)	85 (2)	0	0
	Ischaemia	86 (6)	84 (6)	76 (9)			
RL (%)	Control	80 (6)	80 (6)	75 (6)	81 (3)	0	0
	Ischaemia	84 (3)	84 (3)	82 (4)			

remained unchanged (increase in afterload prevented by aortic unloading), whereas an increase in τ was observed when volume loading increased both end-diastolic and peak systolic left ventricular pressure. However, despite an increase in peak systolic pressure in the present investigation, alterations in circulating blood volume did not affect τ. The load-dependence, if any, of the time constant of isovolumic relaxation during myocardial ischaemia has not been investigated thoroughly. Our results demonstrated that modest alterations in preload had no significant effect on the ischaemia-induced increase in τ.

REGIONAL DIFFERENCES IN DIASTOLIC FUNCTION

In agreement with a previous report [12], the present investigation demonstrated that baseline PLR was higher in the apex than in the base. In addition, we found a significantly shorter relaxation time at the base compared with the apex. Similarly, an isolated increase in left atrial pressure after mitral valve opening has been found to be associated with a significantly greater effect on the segmental PLR in apical compared with mid-wall or posterior myocardium [21]. Taken together, findings from the present and previous [12, 21] investigations indicate that inter-regional differences in segmental wall motion are not confined solely to the ejection period [22].

In the absence of myocardial ischaemia, alterations in circulating blood volume had no effect on PLR or on the percentage of lengthening during the rapid phase in both apical and basal myocardium. Similar findings were reported by Lew and LeWinter [12]. In contrast, Bahler and Martin demonstrated that acute reductions in preload (caval occlusion) were associated with proportional reductions in the peak rate of early diastolic re-extension and in the relaxation time measured in the internal short axis (midway between the apex and base) [11]. In addition, Ishida and colleagues found a 20% increase in peak transmitral flow rate after volume loading had increased end-diastolic pressure over a range similar to that of the present study (9.4–13.3 mm Hg) [23]. However, these apparently contradictory findings may simply result from assessment of regional function in a circumferential plane in the present study. Assuming that at the site of the crystals, the left ventricle may be regarded as a cylindrical annulus, changes in the area of the cavity and hence intra-cavitary volume (V), are proportional to the square of the measured subendocardial circumferential length ($V = kL^2$). Thus the change in volume ($\mathrm{d}V$) which corresponds to any change in length ($\mathrm{d}L$) depends on the instantaneous length ($\mathrm{d}V/\mathrm{d}t = 2kL \times \mathrm{d}L/\mathrm{d}t$). Accordingly, in the presence of an unchanged peak segmental lengthening rate the peak rate of volume change is proportional to $2L$. Thus the 10% increase in segmental length, brought about by volume modification under control conditions, is compatible with a 20% increase in $\mathrm{d}V/\mathrm{d}t$ found by Ishida and colleagues [23] in their study involving similar modification of left ventricular end-diastolic pressure.

DIASTOLIC FUNCTION OF ISCHAEMIC MYOCARDIUM

A decrease in the peak rate of regional wall thinning or PLR, or both, was demonstrated in an area subjected to exercise-induced ischaemia, pacing-induced ischaemia or flow deprivation as a result of coronary occlusion [24–27]. Whereas the effect of alterations in preload on re-extension in normally perfused myocardium has been investigated [11, 12], the present study is the first to demonstrate that moderate alterations in preload have no significant effect on ischaemia-induced changes in the pattern of segmental lengthening in ischaemic myocardium.

In the ischaemic area, myocardial ischaemia was associated with a reduction in the fraction of lengthening during the rapid phase. This finding, which was not influenced significantly by alterations in circulating blood volume, is compatible with a decrease in the early-to-late peak transmitral flow velocity (E-to-A ratio) which is found commonly in patients with coronary artery disease [28]. In contrast, the relaxation time [11] proved to be insensitive to both ischaemia and volume modification.

DIASTOLIC FUNCTION OF REMOTE NON-ISCHAEMIC MYOCARDIUM

Our results are in agreement with the findings of an earlier study from our laboratory that demonstrated an earlier onset and a decrease in maximal lengthening rate of non-ischaemic segments during coronary occlusions in anaesthetized dogs [29]. In contrast, Nonogi and colleagues demonstrated an increase in PLR of the non-ischaemic area during exercise-induced ischaemia in patients with coronary artery disease [30]. No such increase in PLR was found by Nakamura and colleagues during pacing-induced angina in patients with coronary artery disease [26]. In the anaesthetized pig, Takahashi, Levine and Grossman found a significant increase in PLR in non-ischaemic myocardium during pacing-induced ischaemia but not during coronary occlusions [27]. Their findings suggest that an increase in heart rate, caused by pacing or exercise, may have an independent effect on PLR in remote non-ischaemic myocardium. Whereas the effects of preload on systolic function in remote non-ischaemic myocardium have been investigated previously [31] the present study is the first to demonstrate the combined effects of myocardial ischaemia and alterations in preload on the regional lengthening pattern of remote non-ischaemic myocardium.

CRITIQUE OF METHODOLOGY

The present investigations were performed in acutely instrumented animals with an open chest and an open pericardium. Therefore, the effects of myocardial ischaemia occurred in the presence of, and may have been modified by, an acute surgical preparation. Our findings were obtained in a model of low-flow ischaemia and, therefore, cannot necessarily be extrapolated to demand-induced ischaemia. At present regional myocardial ischaemia can neither qualitatively nor quantitatively be defined using indices of diastolic (dys)function; we therefore defined ischaemia using a systolic wall motion abnormality (systolic lengthening) and ensured the presence of severe myocardial ischaemia during the whole loading procedure. However, as the extent of systolic dysfunction (segmental shortening) was more marked than that of diastolic dysfunction (segmental shortening), further studies are necessary to determine if and how our findings may be modified in the settings of mild or moderate ischaemia. In agreement with a previous study from our laboratory [32], we found that systolic lengthening was related inversely to preload. As it is unlikely that our loading procedure altered the passive properties of severely ischaemic myocardium, our observation may relate to the combined effects of preload and stretch caused by the shortening of non-ischaemic segments during the period of isovolumic contraction: in the presence of a low preload the ischaemic segment is situated on the flat part of its pressure–length relation and further lengthening is easily accomplished during isovolumic contraction. In contrast, further lengthening is difficult to achieve when a high preload has already placed the ischaemic segment on the steep part of its pressure–length relation.

The regional pattern of lengthening was obtained from sonomicrometers implanted in a circumferential plane. Depending on the ventricular region, uniaxial measurements may underestimate the extent of both shortening and re-extension [33]. However, shortening and lengthening in the apical region of the anterior wall occurs predominantly in a circumferential plane [33]. To the best of our knowledge, the preferential plane(s) of regional deformations in basal areas of the anterior wall have not been described and, therefore, inter-regional comparisons have to be interpreted with caution.

General linear interactive modelling was used to assess the combined effects of myocardial ischaemia and alterations in circulating blood volume on dependent variables. In addition to identifying significant terms and interactions, this statistical method yields variable estimates which allow quantitative assessment of independent predictors. For example, the parameter estimates for the combined effects of ischaemia, peak ventricular pressure, and volume on $-dP/dt$ (see results) indicate that a similar decrease in $-dP/dt$ may be achieved by imposing myocardial ischaemia (-267 mm Hg s^{-1}) or by lowering the peak ventricular pressure by 11 mm Hg (-11×24 mm Hg s^{-1}).

IMPLICATIONS

As left ventricular diastolic function appears to be particularly sensitive to myocardial ischaemia, monitoring diastolic function may prove to be appropriate to detect and monitor perioperative myocardial ischaemia. However, in the perioperative period alterations in preload are common and, therefore, indices of diastolic function should be insensitive to alterations in circulating blood volume. Previous studies have demonstrated that moderate alterations in preload (changes in end-diastolic pressure ±4–5 mm Hg), caused by nitroglycerin or ventriculography, may mimic or mask diastolic dysfunction, as assessed by indices derived from the mitral inflow velocity profile [7, 8]. The present results suggest that indices derived from left ventricular pressure measurements are also of limited value: peak negative dP/dt is preload-dependent and appears to reflect ischaemia-induced changes in contractility rather than relaxation. Absolute values for τ, although preload-independent, failed to distinguish between ischaemia and control. However, our findings demonstrate that the pattern of segmental lengthening, while being sensitive to myocardial ischaemia, is not affected by alterations in preload. This suggests that the non-invasive monitoring of early segmental lengthening rather than flow profile or indices derived from left ventricular pressure may be useful for the detection and assessment of myocardial ischaemia. Further studies are necessary to determine if in the presence of other types of ischaemia (e.g. moderate low-flow ischaemia, demand-induced ischaemia) segmental lengthening is also sensitive to ischaemia and insensitive to alterations in preload. Moreover, clinical investigations (e.g. perioperative echocardiography) need to demonstrate if monitoring of the regional pattern of early lengthening is feasible and offers any advantage over the currently used monitoring of regional contractile function.

Acknowledgements

Supported by grant No. G9102838SA from the Medical Research Council; Dr Dalmas was supported by the ICI Grant of the European Academy of Anaesthesiology; Dr Marsch was supported by a Fellowship of the Swiss National Foundation for Biological and Medical Sciences; Dr Philbin was supported by Senior International Fellowship 1F06TW01699-01, Fogarty Center, NIH, USA; Dr Gavaghan was supported by a Fellowship of the Wellcome Trust.

References

1. Dodek A, Kassebaum DG, Bristow JD. Pulmonary edema in coronary artery disease without cardiomegaly: Paradox of the stiff heart. *New England Journal of Medicine* 1972; **286**: 1347–1350.
2. Bonow RO, Bacherach SL, Green MV, Kent KM, Rosing DR, Lipson LC, Leon MB, Epstein SE. Impaired left ventricular diastolic filling in patients with coronary artery disease. Assessment with radionuclide angiography. *Circulation* 1981; **64**: 315–323.
3. Aroesty JM, McKay RG, Heller GV, Royal HD, Als AV, Grossman W. Simultaneous assessment of left ventricular systolic and diastolic dysfunction during pacing-induced ischemia. *Circulation* 1985; **5**: 889–900.
4. Doyle RL, Foëx P, Ryder WA, Jones LA. Differences in ischaemic dysfunction following gradual vs abrupt coronary occlusions: Effects on isovolumic relaxation. *Cardiovascular Research* 1987; **21**: 507–514.
5. Paulus WJ, Grossmann W, Serizawa T, Bourdillon PD, Pasipoularides A, Mirsky I. Different effects of two types of ischemia on myocardial systolic and diastolic function. *American Journal of Physiology* (*Heart Circ Physiol 17*) 1985; **248**: H719–H729.
6. Mangano DT. Perioperative cardiac morbidity. *Anesthesiology* 1990; **72**: 153–184.
7. Choong CY, Herrmann HC, Weyman AE, Fifer MA. Preload dependence of Doppler-derived indexes of left ventricular diastolic function in humans. *Journal of the American College of Cardiology* 1987; **10**: 800–808.
8. Stoddard MF, Pearson AC, Kern MJ, Ratcliff J, Mrosek DG, Labovitz AJ. Influence of alteration in preload on the pattern

of left ventricular diastolic filling as assessed by Doppler echocardiography in humans. *Circulation* 1989; **79**: 1226–1236.

9. Weiss JL, Frederiksen JM, Weisfeldt ML. Hemodynamic determinants of the time-course of fall in canine left ventricular pressure. *Journal of Clinical Investigation* 1976; **58**: 751–776.
10. Yellin EL, Hori M, Yoran C, Sonnenblick EH, Gabbay S, Frater RWM. Left venticular relaxation in the filling and nonfilling intact canine heart. *American Journal of Physiology* (*Heart Circ Physiol 19*) 1986; **250**: H620–H629.
11. Bahler RC, Martin P. Effects of loading conditions and inotropic state on rapid filling phase of left ventricle. *American Journal of Physiology* (*Heart Circ Physiol 17*) 1985; **248**: H523–H533.
12. Lew WYW, LeWinter MM. Regional circumferential lengthening patterns in canine left ventricle. *American Journal of Physiology* (*Heart Circ Physiol 14*) 1983; **245**: H741–H748.
13. Hess OM, Osakada G, Lavelle JF, Gallagher KP, Kemper WS, Ross J jr. Diastolic myocardial wall stiffness and relaxation during partial and complete coronary occlusions in the conscious dog. *Circulation Research* 1983; **52**: 387–400.
14. De Bruyne B, Bonzwaer JGF, Heyndrickx GR, Paulus WJ. Comparative effects of ischemia and hypoxemia on left ventricular systolic and diastolic function in humans. *Circulation* 1993; **88**: 461–471.
15. Cohn PF, Liedtke AJ, Serur J, Sonnenblick EH, Urschel CW. Maximal rate of pressure fall (peak negative dP/dt) during ventricular relaxation. *Cardiovascular Research* 1972; **6**: 263–267.
16. Weisfeldt ML, Scully HE, Frederiksen J, Rubenstein JJ, Pohost GM, Beierholm E, Bello AG, Daggett WM. Hemodynamic determinants of maximum negative dP/dt and periods of diastole. *American Journal of Physiology* 1974; **227**: 613–621.
17. Gaasch WH, Blaustein AS, Andrias CW, Donahue RP, Avitall B. Myocardial relaxation: II. Hemodynamic determinants of rate of left ventricular isovolumic pressure decline. *American Journal of Physiology* (*Heart Circ Physiol 8*) 1980; **239**: H1–H6.
18. Karliner JS, LeWinter MM, Mahler F, Engler R, O'Rourke RA. Pharmacologic and hemodynamic influences on the rate of isovolumic left ventricular relaxation in the normal conscious dog. *Journal of Clinical Investigation* 1977; **60**: 511–522.
19. Raff GL, Glantz SA. Volume loading slows left ventricular isovolumic relaxation rate. Evidence of load-dependent relaxation in the intact dog heart. *Circulation Research* 1981; **48**: 813–824.
20. Gaasch WH, Carroll JD, Blaustein AS, Bing OL. Myocardial relaxation: effects of preload on the time course of isovolumetric relaxation. *Circulation* 1986; **73**: 1037–1041.
21. Hoit BD, LeWinter M, Lew WYW. Independent influence of left atrial pressure on regional peak lengthening rates. *American Journal of Physiology* (*Heart Circ Physiol 28*) 1990; **259**: H480–H487.
22. Diedericks J, Leone BJ, Foëx P. Regional differences in left ventricular wall motion in the anesthetized dog. *Anesthesiology* 1989; **72**: 82–90.
23. Ishida Y, Meisner JS, Tsujioka K, Gallo JI, Yoran C, Frater RWM, Yellin EL. Left ventricular filling dynamics: Influence of left ventricular relaxation and left atrial pressure. *Circulation* 1986; **74**: 36–44.
24. Mason SJ, Weiss JL, Weisfeldt ML, Garrison JB, Fortuin NJ. Exercise echocardiography: detection of wall motion abnormalities during ischemia. *Circulation* 1979; **59**: 50–59.
25. Bourdillon PD, Lorell BH, Mirsky I, Paulus WJ, Wynne J, Grossman W. Increased regional myocardial stiffness of the left ventricle during pacing-induced angina in man. *Circulation* 1983; **67**: 316–323.
26. Nakamura Y, Sasayama S, Nonogi H, Murakami T, Kawai C. Alterations in left ventricular relaxation, early diastolic filling and passive viscoelastic properties during postpacing ischemia. *American Journal of Cardiology* 1989; **63**: 72E–77E.
27. Takahashi T, Levine MJ, Grossman W. Regional diastolic mechanics of ischemic and non-ischemic myocardium in the pig heart. *Journal of the American College of Cardiology* 1991; **17**: 1203–1212.
28. Iliceto S, Amico A, Marangelli V, D'Ambrosio G, Rizzon P. Doppler echocardiographic evaluation of the effect of atrial pacing-induced ischemia on left ventricular filling in patients with coronary artery disease. *Journal of the American College of Cardiology* 1988; **11**: 953–961.
29. Meyer TE, Foëx P, Ryder WA. Regional interaction and its effect on patterns of myocardial segmental shortening and lengthening during different models of asynchronous contraction in the dog. *Journal of the American College of Cardiology* 1992; **26**: 476–486.
30. Nonogi H, Hess OM, Bortone AS, Ritter M, Caroll JD, Krayenbuehl HP. Left ventricular pressure–length relation during exercise-induced ischemia. *Journal of the American College of Cardiology* 1989; **13**: 1062–1070.
31. Noma S, Askenase AD, Weintraub WS, Klein LW, Agarwal JB, Helfant RH. Augmentation of contraction in remote nonischemic zone during acute ischemia. *American Journal of Physiology* (*Heart Circ Physiol 24*) 1988; **255**: H301–H310.
32. Dalmas S, Wanigasekera VA, Marsch SCU, Ryder WA, Wong LSS, Foëx P. The influence of preload on post-systolic shortening in ischaemic myocardium. *European Journal of Anaesthesiology* 1995; **12**: 127–133.
33. Villarreal FJ, Lew WYW. Finite strains in anterior and posterior wall of canine left ventricle. *American Journal of Physiology* (*Heart Circ Physiol 28*) 1990; **259**: H1409–H1418.

British Journal of Anaesthesia 1996; **76**: 428–434

Effects of carbon dioxide embolism with nitrous oxide in the inspired gas in piglets†

J.-B. NYARWAYA, S. PIERRE, J.-X. MAZOIT, V. UMBRAIN, M. ROMAIN, K. SAMII AND A. D'HOLLANDER

Summary

We have compared cardiorespiratory variables in anaesthetized piglets whose lungs were ventilated with oxygen in nitrous oxide (N_2O group) or nitrogen (N group) after right ventricular carbon dioxide boluses (0.5 or 1 ml kg^{-1}; $n = 12$) or slow graded injections ($n = 6$). Boluses affected all variables studied significantly ($P < 0.05$) except mean systolic arterial pressure. Significant changes in PE'_{CO_2} ($P = 0.012$) and Pa_{O_2} ($P = 0.048$) values were observed in the N_2O group. Changes in Pa_{CO_2} were related to volumes of injected carbon dioxide ($P = 0.044$). Boluses of 1.0 ml kg^{-1} induced severe circulatory collapse in two piglets in the N_2O group. Slow embolization altered respiratory variables significantly ($P < 0.001$)). Pa_{O_2} decreased significantly in the N_2O group ($P < 0.0001$). Mean pulmonary arterial pressure increased significantly over time ($P = 0.0001$) and lasted longer in the N_2O group ($P < 0.05$). Volumes and time required to induce a 50% increase in mean pulmonary arterial pressure differed significantly between groups ($P < 0.05$). We conclude that nitrous oxide worsened the effects of rapid and slow carbon dioxide emboli on cardiopulmonary variables. Rapid carbon dioxide embolism altered respiratory and haemodynamic variables, while slow carbon dioxide embolism changed only respiratory variables. (*Br. J. Anaesth.* 1996; **76**: 428–434)

Key words

Carbon dioxide, embolism. Anaesthetics gases, nitrous oxide. Embolism, carbon dioxide. Pig.

Cases of carbon dioxide embolism with life-threatening consequences have been reported during laparoscopic surgery [1, 2]. As with air embolism, a variety of factors including the volume of the bolus [3, 4], its rate of entry into the vascular compartment and the inspired gas composition [5–8] are likely to determine the consequences of carbon dioxide embolism. In an *in-vitro* experiment, Nunn [5] noticed that air bubbles enlarged when infused in blood obtained from a patient whose lungs had been ventilated with nitrous oxide–oxygen mixtures. Steffey, Johnson and Eger [9] observed that breathing nitrous oxide resulted in significantly greater and prolonged increases in mean pulmonary artery pressure (PAP) after i.v. injection of carbon dioxide in anaesthetized dogs. These observations [5, 9] suggest that nitrous oxide diffuses from the surrounding blood and alveolar space into the carbon dioxide bubbles as they travel through the venous and pulmonary circulation.

In the present study we have examined the influence of volume and rate of entry into the right ventricle of carbon dioxide emboli, and the role of the inspired gas (nitrous oxide–oxygen *vs* nitrogen–oxygen) on both haemodynamic state and gas exchange in anaesthetized piglets. Two different experimental conditions were studied: boluses and slow graded infusions of carbon dioxide. These models were intended to mimic either an acute carbon dioxide embolism or a progressive gas embolism, as might be produced by carbon dioxide passing through a venous tear during laparoscopic procedures.

Materials and methods

We studied domestic piglets (Belgian Pietrain) of both sexes ($n = 18$) weighing 23–27 kg after obtaining approval from the Animal Research Committee of Erasme University Hospital, Brussels.

Fasting animals were premedicated with azaperone 1 mg kg^{-1} i.m. and anaesthetized with a combination of ketamine 20 mg kg^{-1} i.m., atropine 0.05 mg kg^{-1} i.m. and midazolam 0.1 mg kg^{-1} i.m. [10]. Tracheal intubation was facilitated with administration of pancuronium 0.5 mg kg^{-1} [11] supplemented with propofol 2–5 mg kg^{-1} [12]. The lungs were ventilated with a Servo Elema 900B ventilator (Siemens, Solna, Sweden). Anaesthesia was maintained with propofol 25 mg kg^{-1} h^{-1} i.v., fentanyl 10 µg kg^{-1} h^{-1} i.v. and pancuronium 0.4 mg kg^{-1} h^{-1} i.v. Fluid infusion of 0.9% NaCl 10 ml kg^{-1} h^{-1} was given via a cannula in the external vein of the ear. Inspired gas composition, end-tidal partial pressure of carbon dioxide (PE'_{CO_2}) and

---

JEAN-BAPTISTE NYARWAYA*, MD, SÉBASTIEN PIERRE§, MD, JEAN-XAVIER MAZOIT*, MD, PHD, VINCENT UMBRAIN‡, MD, MIREILLE ROMAIN§, KAMRAN SAMII*, MD, ALAIN D'HOLLANDER§, MD, PHD, Experimental Laboratory of the Department of Anaesthesiology, CUB Erasme, 808 Route de Lennik, 1070 Brussels, Belgium.

Accepted for publication: November 6, 1995.

Present addresses:

*CHU Bicêtre, France.

‡AZVUB, Brussels, Belgium.

§Free University of Brussels, Brussels, Belgium.

†Presented in part at The Second Congress of the European Society of Anaesthesiologists, February 9, 1994, Brussels, Belgium.

Correspondence to A. d'H.

ventilation rate were monitored continuously using a Datex Capnomac AGM-103 monitor (Datex, Helsinki, Finland). Tidal volume, temperature and pulse oximetry (Sp_{O_2}) were monitored using a Datex Cardiomap Ultima SV monitor (Datex, Helsinki, Finland).

The saphenous artery was cannulated for recording of systemic artery pressure and sampling for arterial blood-gas analysis. Both external jugular veins were dissected for the introduction of catheters. A flow-directed thermodilution catheter (7.5 Fr, Edwards Swan-Ganz, Baxter Healthcare Co, Irvine, CA, USA) was placed in the pulmonary artery for continuous monitoring of PAP and measurements of cardiac output (CO). A second flow-directed thermodilution catheter (7.5 Fr, Edwards Swan-Ganz, Baxter Healthcare Co, Irvine, CA, USA) and a double-lumen catheter (7 Fr, Deltacath, Becton Dickinson, USA) were introduced into the right ventricle and auricle, respectively, via the opposite external jugular vein. The position of the catheters was confirmed by the presence of an appropriate pressure-wave pattern on the monitor. Systolic arterial pressure (SAP) and PAP were measured continuously using electronic transducers (Uniflow, Baxter Healthcare Co, Uden, Holland) connected to a monitoring system (Sirecust 404-1, Siemens AG, Erlangen, Germany) with zero pressure at the thoracic mid-level as the reference. A 2-MHz Doppler ultrasonic flow transducer (Sonicaid Model D206, Oxford Sonicaid Ltd, Chichester, UK) was positioned above the right heart chambers so that a 10-ml saline injection delivered to the right ventricle would produce an audible change in sound.

A record of the ECG, ultrasonic Doppler signal, $P\text{E}'_{CO_2}$, SAP and PAP was obtained on a six-channel recorder (Model 800, Gould Electronic, Baillanvilliers, France) for later analysis of these variables. Arterial blood-gas values were determined using an ABL 500 (Radiometer, Copenhagen, Denmark). Measurements of CO were performed in triplicate using a SAT-1 cardiac output computer (American Edwards Lab., Irvine, CA, USA) with 10-ml injections of 0.9 % NaCl via one port of the double-lumen catheter.

The fractional inspired concentration of oxygen ($F\text{I}_{O_2}$) was set at 0.32–0.35 and ventilation adjusted to maintain the arterial partial pressure of carbon dioxide (Pa_{CO_2}) at 4.5–6 kPa. The animal's core temperature was monitored via a pulmonary artery thermocouple and maintained at 38–39.5 °C throughout the experiment. Acquisition of baseline data began after a stabilization period of at least 30 min after completion of the surgical procedure. Variables monitored included Sp_{O_2}, Sa_{O_2}, Pa_{O_2}, $P\text{E}'_{CO_2}$, Pa_{CO_2}, heart rate (HR), mean SAP, mean PAP and CO.

STUDY 1: RAPID CARBON DIOXIDE BOLUS INJECTION

Twelve piglets were allocated randomly in one of two groups to undergo ventilation with either oxygen–nitrogen (N_2 group, $n = 6$) or oxygen–nitrous oxide (N_2O group, $n = 6$) mixture. The carbon dioxide gas was delivered from a container with outflow pressure and volume regulated by a manometer connected to a 50-ml leak-free syringe. A three-way stopcock enabled the syringe to be connected between the outflow tubing of the carbon dioxide container and the distal port of the 7.5-French gauge thermodilution catheter for embolization. Before embolization, the syringe was flushed five times with carbon dioxide. The injection was then performed manually over a 30-s period. Animals were injected successively with two carbon dioxide volumes (0.5 and 1 ml kg^{-1}) following a crossover design.

STUDY 2: SLOW GRADED INJECTIONS

A manually regulated flowmeter (Aalborg Instruments, Monsey, NY, USA) mounted between the manometer of the carbon dioxide container and the distal port of the 7.5-French gauge flow-directed catheter was used to adjust the volume infused per minute. Piglets were embolized with a gradual increase in carbon dioxide flow while the lungs were ventilated with either oxygen–nitrogen (N_2 group, $n = 6$) or oxygen–nitrous oxide (N_2O group, $n = 6$). The infusion was discontinued when mean PAP increased by 50 % from baseline. Initially, piglets were embolized with a carbon dioxide flow of 7.5 ml min^{-1}. At each increment, the embolized carbon dioxide volumes were increased by 10 graduations and the infusion was maintained for 3 min at a constant pressure of 14.7 psi. A calibration chart allowed determination of the infused carbon dioxide flows according to readings wherein 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 corresponded to 7.5, 12.6, 17.5, 24, 31, 39.4, 49, 58.4, 69.5, 82.1 ml min^{-1}, respectively.

Between the experimental sequences, the blood-gas variables studied were allowed to return to control values. Ventilation with different gas mixtures was separated by 1 h of ventilation with 100 % oxygen to ensure adequate washout of nitrous oxide and nitrogen. Thereafter, a 30 min-period of washing with either nitrogen or nitrous oxide was allowed before the next experiment was performed.

STATISTICAL ANALYSIS

Study 1

All variables were analysed using a three-way (time, nitrous oxide *vs* nitrogen, 0.5 *vs* 1 ml kg^{-1}) analysis of variance (ANOVA) with one-way (time) for repeated measurements. The Newman–Keuls test was used for multiple comparisons where appropriate.

Study 2

A two-way (time and nitrous oxide *vs* nitrogen) ANOVA with one-way for repeated measurements (time) was carried out. The Newman–Keuls test was used for multiple comparisons when applicable. The volume of carbon dioxide required to induce an increase of 50 % in mean PAP, duration of injection and the time to recovery of basal $P\text{E}'_{CO_2}$ values were compared between groups using the Wilcoxon test for paired data [13].

Data are expressed as mean (SD). Changes were considered statistically significant at $P < 0.05$.

Results

Baseline values of the variables after anaesthesia are shown in table 1.

Table 1 Baseline values of studied variables (36 measurements) recorded from six groups of piglets ($n = 6$ in each group) after anaesthesia and ventilation of the lungs with 35% oxygen and either nitrogen or nitrous oxide

	Mean	Range	SD
HR (beat min^{-1})	119	110–130	6
Mean SAP (mm Hg)	96	83–110	10
Mean PAP (mm Hg)	20	17–24	2
CO (litre min^{-1})	3080	2800–3500	240
Sp_{O_2} (%)	96	95–97	1
Sa_{O_2} (%)	97	96–97	1.5
Pa_{O_2} (kPa)	17.4	15.2–18.4	1.1
$P\text{E}'_{CO_2}$ (kPa)	5	4.6–5.3	0.3
Pa_{CO_2} (kPa)	5.3	5.3–5.6	0.1

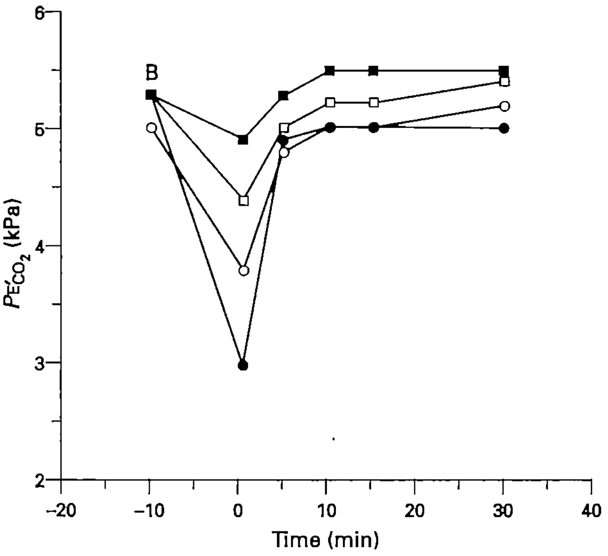


Figure 1 Effect of carbon dioxide embolism on $P\text{E}'_{CO_2}$ in the N_2 group after 0.5 ml kg^{-1} (■) and 1 ml kg^{-1} (□) boluses, and in the N_2O group after 0.5 ml kg^{-1} (●) and 1 ml kg^{-1} (○) boluses against time.

STUDY 1

In all animals, precordial sensor-detected carbon dioxide embolism occurred in less than 5 s after injection of carbon dioxide boluses.

Changes in gas exchange

After embolization, $P\text{E}'_{CO_2}$ decreased significantly over time ($P = 0.001$, ANOVA) and these reductions were more severe in the N_2O group than in the N_2 group ($P = 0.012$, ANOVA). However, there were no statistically significant differences between the two volumes of carbon dioxide boluses (0.5 *vs* 1 ml kg^{-1}).

At $T + 30$ s, the changes in $P\text{E}'_{CO_2}$ were decreased significantly in all groups ($P < 0.05$, Newman-Keuls test) (fig. 1). In three piglets in the N_2 group, analysis of recording charts showed an increase in $P\text{E}'_{CO_2}$ up to a mean of 0.3 kPa after embolization with 0.5 ml kg^{-1}. These initial increases lasted about 20 s and were followed by typical post-embolic $P\text{E}'_{CO_2}$ decreases (fig. 2).

Changes in Sp_{O_2} and Sa_{O_2} were time related ($P = 0.001$, ANOVA). Decreases in Sp_{O_2} and Sa_{O_2} values were greatest at $T + 0.5$ min ($P < 0.05$, Newman–Keuls test) compared with other times. Sp_{O_2} decreased by 5% and 9% after 0.5 and 1 ml kg^{-1} boluses, respectively, but only in the N_2O groups (fig. 3). Sa_{O_2} and Sp_{O_2} did not differ significantly with different inhaled gas mixtures and volumes of carbon dioxide boluses.

Alterations in Pa_{O_2} were significant in relation to time ($P = 0.0001$) and were more severe in the N_2O than in the N_2 group ($P = 0.048$, ANOVA). In the N_2 and N_2O groups, Pa_{O_2} decreased to 81% and 71% from baseline after 0.5 ml kg^{-1} carbon dioxide boluses, while after embolization with 1 ml kg^{-1} decreases to 72% and 59% were observed. With 1 ml kg^{-1} carbon dioxide boluses, decreased Pa_{O_2} persisted for 30 min in the N_2O group.

Differences in Pa_{CO_2} were significant in relation to time ($P = 0.0001$, ANOVA) and to volumes of carbon dioxide boluses ($P = 0.044$, ANOVA). In both groups, Pa_{CO_2} values returned to baseline 30 min after embolization and no significant difference was observed in relation to gas mixture.

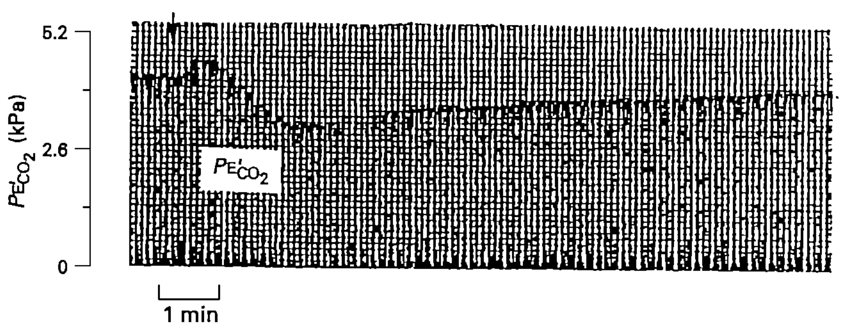


Figure 2 A typical tracing showing an increase in $P\text{E}'_{CO_2}$ and a subsequent decrease after right intraventricular embolization with 0.5 ml kg^{-1} following ventilation with an oxygen–nitrogen mixture in piglet No. 5. The arrow indicates the beginning of the right intraventricular emergence of the carbon dioxide bubbles.

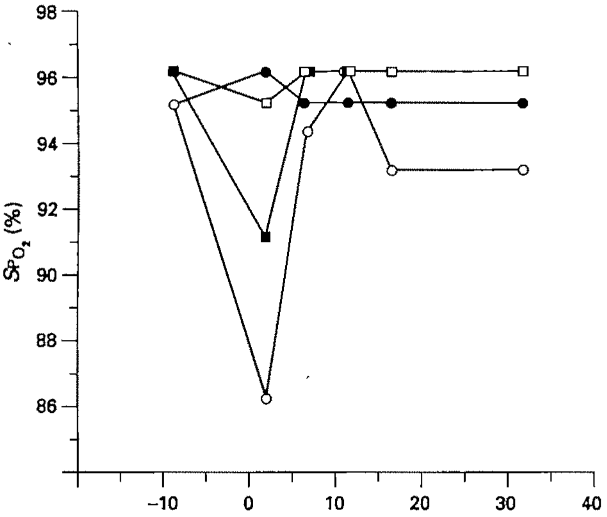


Figure 3 Evolution of Sp_{O_2} from baseline values against time in the N_2 groups after 0.5 ml kg^{-1} (■) and 1 ml kg^{-1} (□), and in the N_2O groups after 0.5 ml kg^{-1} (●) and 1 ml kg^{-1} (○) carbon dioxide boluses. All values are mean ($n = 6$ in each group).

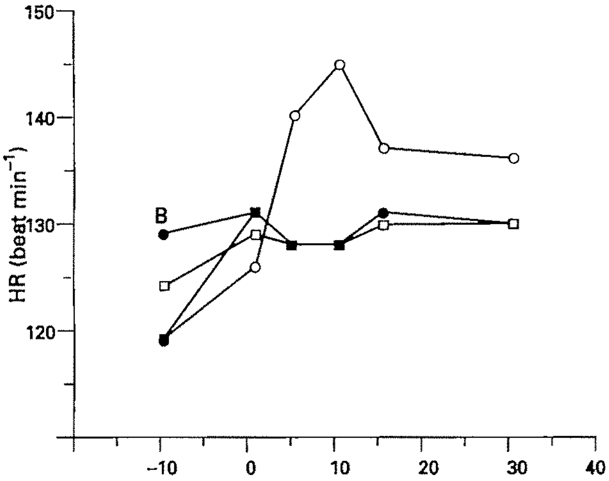


Figure 4 Changes in heart rate (HR) from baselines values in the N_2 groups after 0.5 ml kg^{-1} (□) and 1 ml kg^{-1} (■) and in the N_2O groups after 0.5 ml kg^{-1} (●) and 1 ml kg^{-1} (○) against time. Note there are increases only in the N_2O groups compared with baseline. All values are mean ($n = 6$ in each group).

Cardiovascular changes

HR changed significantly over the post-embolization periods ($P = 0.029$, ANOVA). At $T+5$ min and $T+10$ min, these differences were significant ($P < 0.05$, Newman–Keuls test) (fig. 4) compared with other periods. No significant changes were observed in MAP values.

Mean PAP changed significantly in relation to time ($P < 0.0001$, ANOVA). These changes were observed at $T+30$ s and $T+5$ min ($P < 0.05$, Newman–Keuls test).

Changes in CO were observed over time ($P < 0.0001$, ANOVA) and differences were significant at $T+30$ s and $T+5$ min ($P < 0.05$, Newman–Keuls test). In the N_2O group, two piglets suffered cardiovascular collapse after embolization with 1 ml kg^{-1} carbon dioxide volumes.

There were no statistically significant differences in relation to the gas mixture used for ventilation and to the two volumes of carbon dioxide boluses (table 2).

Table 2 Statistical significance of changes in the variables studied after rapid carbon dioxide embolization ($n = 6$ in each group)

	Time	N_2 *vs* N_2O	0.5 *vs* 1 ml kg^{-1}
$P\acute{E}_{CO_2}$	0.001	0.012	ns
Sp_{O_2}	0.0001	ns	ns
Sa_{O_2}	0.0001	ns	ns
Pa_{O_2}	0.0001	0.48	ns
Pa_{CO_2}	0.0001	ns	0.044
HR	0.04	ns	ns
Mean SAP	ns	ns	ns
Mean PAP	0.01	ns	ns
CO	0.001	ns	ns

STUDY 2

An increase in mean PAP of 50 % was used as the reference for completion of embolization. Compared with the N_2O group, the N_2 group required higher cumulative infused carbon dioxide volumes (247 (189) ml *vs* 72 (60) ml) and a longer delay to reach a 50 % increase in mean PAP (15.5 (7.6) min *vs* 6.5 (3) min, $P < 0.05$: paired Wilcoxon test) (fig. 5).

Changes in gas exchange

After embolization, $P\acute{E}_{CO_2}$ changed significantly with time ($P = 0.001$, ANOVA). At $T+30$ s, $P\acute{E}_{CO_2}$ showed significant decreases of 20 % in the N_2 group *vs* 27 % in the N_2O group ($P < 0.05$, Newman–Keuls test). The time to regain baseline $P\acute{E}_{CO_2}$ values was longer in the N_2 group than in the N_2O group (11.5 (7.6) min *vs* 7 (4) min, $P < 0.05$: unpaired Wilcoxon's test). The chart recording of $P\acute{E}_{CO_2}$ during slow embolization showed a plateau profile, despite the stepwise variation in the delivery of carbon dioxide flows used for embolization (fig. 6).

We found significant post-embolic decreases in Sp_{O_2} and Sa_{O_2} over time ($P < 0.0001$) in both groups and the differences were significant at $T+30$ s ($P < 0.05$, Newman–Keuls test).

Values of Pa_{O_2} decreased significantly ($P < 0.0001$, ANOVA) by 70 % and 63 % from baseline in the N_2 and N_2O groups ($P < 0.05$, Newman–Keuls test), respectively, at $T+30$ s.

Post-embolic increases of 24 % in Pa_{CO_2} ($P < 0.0001$, ANOVA) were noted at $T+30$ s in both groups.

Cardiovascular changes

There were no statistically significant changes in HR, mean SAP and CO with time (table 3). Only mean PAP values changed significantly over time ($P = 0.01$, ANOVA). At $T+30$ s and $T+5$ min, mean PAP values were significantly greater than those recorded at other times ($P < 0.05$, Newman-Keuls test). Thirty minutes after termination of

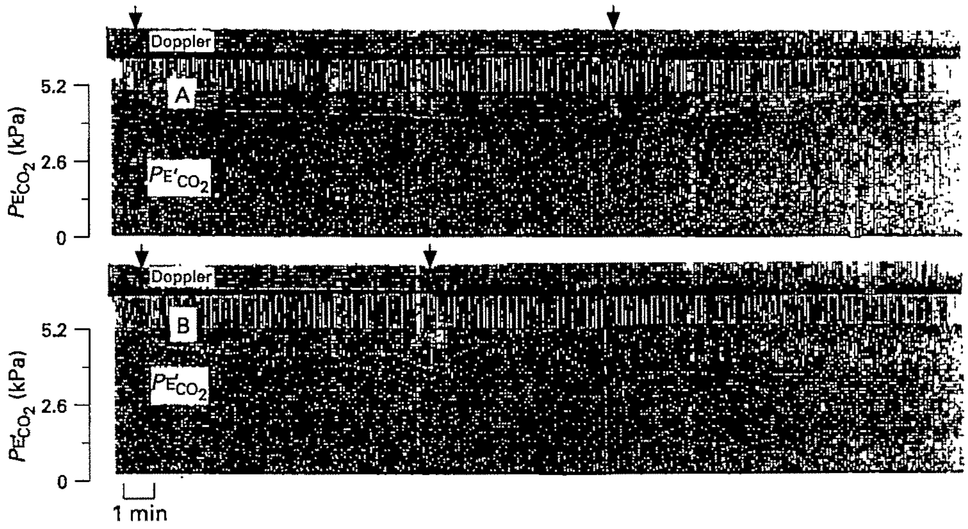


Figure 5 Typical tracings showing changes in PE'_{CO_2} and the Doppler signal after slow right intraventricular embolization with slow graded carbon dioxide infusion during ventilation with oxygen–nitrogen (A) or oxygen–nitrous oxide (B) in piglet No. 3. The arrows indicate the beginning and end of right intraventricular emergence of the carbon dioxide bubbles.

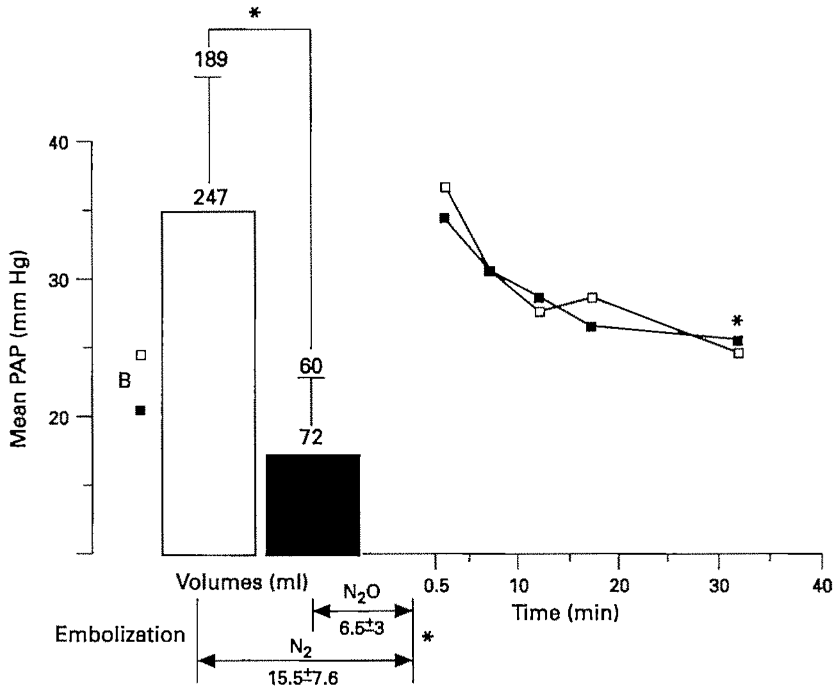


Figure 6 Evolution of mean PAP from baseline values (B) after slow intraventricular embolization with graded carbon dioxide infusion during ventilation with oxygen–nitrogen (□) or oxygen–nitrous oxide (■). Injected volumes in the nitrous oxide (□) *vs* the N_2 group (■) and time (N_2O *vs* N_2) required to obtain a 50% increase in mean PAP are shown. All values are mean (SD), * $P < 0.05$ ($n = 6$ in each group).

Table 3 Statistical significance of changes in the variables studied after slow carbon dioxide embolization ($n = 6$ in each group)

	Time	O_2/N_2 *vs* O_2/N_2O
PE'_{CO_2}	0.001	ns
Sp_{O_2}	0.001	ns
Sa_{O_2}	0.001	ns
Pa_{O_2}	0.001	ns
Pa_{CO_2}	0.001	ns
HR	ns	ns
Mean SAP	ns	ns
Mean PAP	0.001	ns
CO	ns	ns

embolization, residual mean PAP increases were still significantly higher (21% *vs* 10% from baseline values, $P < 0.05$) in the N_2O group than in the N_2 group (fig. 5).

Discussion

We have shown that after rapid and progressive carbon dioxide embolism in piglets, cardiorespiratory alterations were worsened by the presence of nitrous oxide in the gas mixture used for mechanical ventilation. These findings confirm the results of previous studies which demonstrated that nitrous oxide amplifies the effects of venous air [6–8] or carbon dioxide embolism and prolongs the delay to recover from the physiological insults [9]. In agreement with previous studies [7, 9], nitrous oxide reduced the volume required to induce predetermined changes.

Continuous $P\text{E}'_{CO_2}$ monitoring showed some particular trends in addition to the commonly observed sharp decrease after gas embolism. First, abrupt and transient increases in $P\text{E}'_{CO_2}$ were observed after rapid boluses of low volume. This observation confirms the biphasic trend of $P\text{E}'_{CO_2}$ recordings reported previously after carbon dioxide embolism during laparoscopic surgery [2, 14, 15]. Second, while mean PAP continued to increase during progressive embolization, $P\text{E}'_{CO_2}$ values decreased steadily and demonstrated a plateau profile. Moreover, $P\text{E}'_{CO_2}$ values returned to baseline earlier than those of mean PAP and reached a higher level than baseline after slow embolization in the N_2 group. These variations in response differed markedly compared with those reported previously after air embolism [16]. Therefore, it must be emphasized that during progressive carbon dioxide embolism, $P\text{E}'_{CO_2}$ monitoring may not allow either early and reliable detection of carbon dioxide embolism or provide relevant quantitative information about the size of the carbon dioxide emboli. The other non-invasive monitorings, including HR and Sp_{O_2}, demonstrated changes in values and trends similar to those reported after laparoscopic carbon dioxide embolism.

For invasive monitoring, only Pa_{O_2} changed significantly in relation to volume of carbon dioxide boluses and the inspired gas mixture during rapid carbon dioxide embolization. After both rapid and progressive infusions, an increase in mean PAP was observed constantly, immediately after injection of carbon dioxide. In agreement with previous studies on the effects of air [6, 8] and carbon dioxide emboli [9], the rate of increase in mean PAP was related closely to the rate of injection, the volume of the carbon dioxide bolus and the nature of the gases used for ventilation. During slow carbon dioxide embolization, although mean PAP was increased by 50% from baseline, no significant changes in CO were observed. In the presence of N_2O, the trends in mean PAP showed higher values without any significant differences. However, its residual values were significantly higher in the piglets whose lungs were ventilated with oxygen–nitrous oxide. This finding confirms the known sensitivity of mean PAP monitoring in detecting gas embolism [16].

Although this model is not strictly similar to the clinical situation, the right intraventricular site for injection was chosen in an attempt to create a better quantitative experimental design for carbon dioxide embolization to observe the relationship between different patterns (volume and rate) and effects. It is well known that gas bubbles introduced into the jugular vein, superior vena cava and right atrium move downwards in some parts of the cardiac cycle and upwards in others [17], and that some fraction of the injected carbon dioxide is absorbed before reaching the pulmonary vasculature.

The haemodynamic changes induced by slow embolization differ from those observed with carbon dioxide boluses, where decreases in CO may be caused mainly by a "bubble-lock" in the right side of the heart. This observation suggests that mechanical block of portions of the pulmonary circulation is only partial but sufficient to contribute to alterations in pulmonary gas exchange. As the arteriole is the major determinant of PAP, one can speculate that an arteriolar effect may be reflected in these changes in PAP [18]. The present study suggests that the post-embolic vascular change may be greater and more prolonged in the presence of nitrous oxide than nitrogen. However, the magnitude of the post-embolic disturbances, may be determined by the combined effect of the size and number of carbon dioxide bubbles. First, a low volume embolism may allow carbon dioxide microbubbles to reach the alveolar capillaries with high alveolar elimination of carbon dioxide and increase in $P\text{E}'_{CO_2}$. This is in agreement with previous reports of an abrupt but transient increase followed by a progressive decrease during carbon dioxide embolism during laparoscopic surgery [2, 14, 15]. Second, larger carbon dioxide bubbles may induce widespread arteriolar block and pulmonary blood flow redistribution resulting in ventilation-to-perfusion ($V\text{A}/Q$) ratio alterations including an increased $V\text{A}/Q$ ratio in the embolized lung [19] associated with opening of intrapulmonary arteriovenous shunts and decreased $V\text{A}/Q$ ratio in the non-embolized area. The majority of air bubbles ejected from the right ventricle are likely to reach the non-dependent branches of the pulmonary arteries [20, 21]. In terms of regional ventilation-to-perfusion distribution, this implies that inhalation of nitrous oxide would worsen the shift of blood flow to dependent regions with a larger pulmonary shunt and greater deadspace resulting in greater decreases in Pa_{O_2} and $P\text{E}'_{CO_2}$ values during rapid embolization.

When differences in solubility and diffusion are considered, the present study agrees with the principle that inhalation of nitrous oxide aggravates existing air and carbon dioxide embolism [22]. The greater partial pressure of carbon dioxide in bubbles compared with surrounding blood and the alveoli results in a direct transfer of carbon dioxide from bubbles to blood with post-embolic increases in Pa_{CO_2} and higher elimination to alveolar space producing an initial increase in $P\text{E}'_{CO_2}$. Furthermore, the progressive return to baseline values observed in the present study is in agreement with Kunkler and King [23] who demonstrated that carbon dioxide bubbles equilibrated rapidly with the surrounding blood gases and revealed large amounts of other gases, by analysis performed within few seconds on undissolved emboli. Second, considering the greater physiological changes observed in the presence of nitrous oxide, transfer of nitrous oxide into carbon dioxide bubbles may be speculated. The Fick equation to spherical bubble flow in the bloodstream suggests that the rate of gas diffusion is directly proportional to Krogh's coefficient (the product of solubility and diffusion) and the partial pressure gradient of diffusion for that gas [8]. The higher Krogh's coefficient for carbon dioxide than for nitrous oxide and nitrogen suggests that carbon dioxide outflow should be faster than inflow of nitrous oxide and nitrogen for a given partial pressure. Therefore, the magnitude of changes observed during nitrous oxide ventilation may be associated with initial entry of nitrous oxide into the carbon dioxide bubbles until equilibration with the surrounding blood and to the resultant longer lifespan for bubbles, allowing a larger number to induce a cumulative effect. In contrast with nitrous oxide, diffusion of nitrogen into carbon dioxide bubbles would be slower, therefore carbon dioxide bubbles might dissipate more rapidly after embolization.

We conclude that during procedures at risk of carbon dioxide embolism, significant gas exchange alterations should be considered as clinically relevant even in the absence of haemodynamic disturbances. Anaesthetists should keep in mind the study of Eger and Saidman [24] demonstrating that the relationship between nitrous oxide blood concentration and the volume increase of air bubbles is exponential and that for a concentration of between 50% to 75% a two- to four-fold increase may be attained. The present study suggests additional limitations about routine $P\text{E}'_{\text{CO}_2}$ monitoring during laparoscopic surgery. The assumptions that $P\text{E}'_{\text{CO}_2}$ monitoring may reliably detect carbon dioxide embolism during laparoscopy with carbon dioxide insufflation should be reconsidered. Because of the increasing number of surgical laparoscopic procedures which may potentially lead to severe gas embolism [1, 2], the presence of Doppler monitoring should be mandatory, as it has been found to be the most sensitive and specific for detection of gas embolism [16, 25].

References

1. Beck DH, McQuillan PJ. Fatal carbon dioxide embolism and severe haemorrhage during laparoscopic salpingectomy. *British Journal of Anaesthesia* 1994; **72**: 243–245.
2. Diakun TA. Carbon dioxide embolism. Successful resuscitation with cardiopulmonary bypass. *Anesthesiology* 1991; **74**: 1151–1153.
3. Graff TD, Arbegast NR, Philips OC, Harris LC, Frazier TM. Gas embolism: a comparative study of air and carbon dioxide as embolic agents in the systemic venous system. *American Journal of Obstetrics and Gynecology* 1959; **78**: 259–265.
4. English JB, Westenskow D, Hodges MR, Stanley TH. Comparison of venous air embolism monitoring methods in supine dogs. *Anesthesiology* 1978; **48**: 425–429.
5. Nunn JF. Controlled respiration in neurosurgical anaesthesia. *Anaesthesia* 1959; **14**: 413–414.
6. Munson ES, Merrick HC. Effect of nitrous oxide on venous air embolism. *Anesthesiology* 1966; **27**: 783–787.
7. Munson ES. Effect of nitrous oxide on the pulmonary circulation during venous air embolism. *Anesthesia and Analgesia* 1971; **50**: 785–793.
8. Presson RG, Kirk KR, Haselby KA, Wagner WW. Effect of ventilation with soluble and diffusible gases on the size of air emboli. *Journal of Applied Physiology* 1991; **70**: 1068–1078.
9. Steffey EP, Johnson BH, Eger EI II. Nitrous oxide intensifies the pulmonary arterial pressure response to venous injection of carbon dioxide in the dog. *Anesthesiology* 1980; **52**: 52–55.
10. Thurmon JC, Benson GJ. Special anesthesia considerations of swine. In: Short CE, ed. *Principles and Practice of Veterinary Anesthesia*. Baltimore: Williams and Wilkins, 1987; 308–322.
11. Muir AW, Marchall RJ. Comparative neuromuscular blocking effects of vecuronium, pancuronium, Org 6368 and suxamethonium in the anaesthetized pig. *British Journal of Anaesthesia* 1987; **59**: 622–629.
12. Adam HK, Glen JB, Hoyle PA. Pharmacokinetics in laboratory animals of ICI 35 868, a new i.v. anaesthetic agent. *British Journal of Anaesthesia* 1980; **52**: 743–746.
13. Altman DG. *Practical Statistics for Medical Research*. London: Chapman and Hall, 1993.
14. Shulman D, Aronson HB. Capnography in the early diagnosis of carbon dioxide embolism during laparoscopy. *Canadian Anaesthetists Society Journal* 1984; **31**: 455–459.
15. McGrath JB, Zimmerman JE, Williams JF, Parmet J. Carbon dioxide treated with hyperbaric oxygen. *Canadian Journal of Anaesthesia* 1989; **36**: 586–589.
16. Glenski JA, Cucchiara RF, Michenfelder TD. Transesophageal echocardiography and transcutaneous O_2 and CO_2 monitoring for detection of venous air embolism. *Anesthesiology* 1986; **64**: 541–545.
17. Martin RW, Colley PS. Evaluation of transesophageal Doppler detection of air embolism in dogs. *Anesthesiology* 1983; **58**: 117–123.
18. Khan MA, Alkalay I, Suetsugu S, Stein M. Acute changes in lung following pulmonary emboli of various gases in dogs. *Journal of Applied Physiology* 1972; **33**: 774–777.
19. Levy SE, Stein M, Totten RS, Bruderman I, Wessler S, Robin ED. Ventilation–perfusion abnormalities in experimental pulmonary embolism. *Journal of Clinical Investigation* 1965; **44**: 1699–1707.
20. Chang HK, Weber ME, Thomson J, Martin RR. Hydrodynamic features of pulmonary air embolism: a model study. *Journal of Applied Physiology* 1979; **47**: 537–543.
21. Chang HK, Delaunois L, Boileau R, Martin RR. Redistribution of pulmonary flow during experimental air embolism. *Journal of Applied Physiology* 1981; **51**: 211–217.
22. Sergysels R, Jasper N, Delaunois L, Chang HK, Martin RR. Effect of ventilation with different gas mixtures on experimental lung air embolism. *Respiratory Physiology* 1978; **34**: 329–343.
23. Kunkler A, King H. Comparison of air, oxygen and carbon dioxide embolization. *Annals of Surgery* 1959; **149**: 95–99.
24. Eger EI II, Saidman LJ. Hazards of nitrous oxide anesthesia in bowel obstruction and pneumothorax. *Anesthesiology* 1965; **26**: 61–66.
25. Couture P, Boudrault D, Derouin M, Allard M, Lepage Y, Girard D, Blaise G. Venous carbon dioxide embolism in pigs: An evaluation of end-tidal carbon dioxide, transesophageal echocardiography, pulmonary artery pressure, and precordial auscultation as monitoring modalities. *Anesthesia and Analgesia* 1994; **79**: 867–873.

British Journal of Anaesthesia 1996; **76**: 435–445

REVIEW ARTICLE

Sevoflurane—a long-awaited volatile anaesthetic

I. SMITH, M. NATHANSON AND P. F. WHITE

In evaluating any newly introduced anaesthetic, it is worth comparing its properties with those of a theoretical "ideal" volatile agent which would have a low solubility in blood to allow for rapid equilibration between delivered concentration and the effect site in the central nervous system (CNS). This would facilitate rapid induction of anaesthesia, allow easier titration of anaesthetic dose to the desired effect during the maintenance period and permit rapid emergence and recovery at the end of anaesthesia. An ideal anaesthetic should also be easy to deliver and devoid of perioperative side effects and toxicity.

Desflurane (Suprane) was the last new volatile anaesthetic introduced into clinical practice in 1992. Although relatively insoluble and easy to titrate during the maintenance period, desflurane is not a practical induction agent because of its irritant effects on the airway. The theoretically improved control over depth of anaesthesia during the maintenance period afforded by desflurane is complicated by its tendency to induce cardiovascular stimulation when the delivered concentration is increased rapidly [16, 85). In addition, desflurane requires unusually complex vaporizer technology for its administration.

Sevoflurane has been in clinical use in Japan since 1990 and has recently gained approval for use in Great Britain, the United States and much of the rest of the world. This review considers the clinical properties of sevoflurane in relation to existing volatile anaesthetics (table 1) and the "ideal" volatile agent.

History of sevoflurane

Research to develop a safe, non-inflammable inhaled anaesthetic agent began in the 1930s when chemists discovered that the substitution of fluorine for other halogens "lowers the boiling point, increases stability, and generally decreases toxicity" [5]. This work was continued by McBee, who used his knowledge of fluorine chemistry gained from working on the "Manhattan" atomic bomb project, to investigate a number of fluorine-containing compounds, none of which was eventually suitable for clinical use. In 1951, Suckling synthesized halothane, and soon the search for other clinically useful fluorine-containing anaesthetics began in earnest. Sevoflurane (fig. 1) was first synthesized in 1968 by Regan at Travenol Laboratories, Illinois, while he was investigating a series of halomethyl polyfluoroisopropyl ethers. The compound was initially reported by his co-workers in 1971 [83]. The group at Travenol went on to describe the results of animal experiments which characterized the important clinical properties of the new anaesthetic [84]. Development was later to be impeded by apparent toxic effects, eventually shown to be a consequence of flawed experimental design [36]. The first volunteer trials, reported by Holaday and Smith in 1981, were encouraging [37]. However, further work was slow because of the problems of biotransformation and stability with soda lime. The volatile anaesthetic isoflurane was felt at the time to be a more suitable drug for commercial development [8]. Baxter Travenol sold the rights to sevoflurane to Anaquest (Ohmeda/BOC), who in turn sold these to Maruishi Company. Maruishi continued research and development, eventually releasing sevoflurane for clinical use in Japan in May 1990. By the end of 1993, an estimated 1 million patients had received sevoflurane [18]. The continuing search for an inhaled agent with rapid induction, emergence and recovery characteristics has stimulated the recent re-examination of sevoflurane. The considerable resources necessary to introduce another volatile anaesthetic into the western marketplace have resulted in the purchase and subsequent development of sevoflurane by a multinational company, namely Abbott Laboratories.

Physical properties of sevoflurane

Sevoflurane is related structurally to isoflurane and enflurane (fig. 1), and not surprisingly shares many of the physical properties of these dugs; (interestingly, desflurane is even more closely related structurally to isoflurane, yet desflurane has quite unique physical properties). Sevoflurane has a boiling point of 58.6 °C and a saturated vapour pressure (SVP) of 160 mm Hg at 20 °C. These values are similar to those of halothane, enflurane and isoflurane. The blood:gas partition coefficient of sevoflurane is 0.69 [78]. This is approximately half

(*Br. J. Anaesth.* 1996; **76**: 435–445)

Key words
Anaesthetics volatile, sevoflurane.

IAN SMITH, BSC, MB, BS, FRCA, Keele University, North Staffordshire Hospitals, Newcastle Road, Stoke-on-Trent, Staffordshire ST4 6QJ. MICHAEL NATHANSON, MB, BS, MRCP, FRCA, Queen's Medical Centre, University of Nottingham, Nottingham. PAUL F. WHITE, PHD, MD, FANZCA, University of Texas Southwestern Medical Center, Dallas, TX, USA.
Correspondence to I. S.

Table 1 Comparison of sevoflurane with existing volatile anaesthetics (scale: 0 = worst, + + + = best)

Property	Halothane	Enflurane	Isoflurane	Desflurane	Sevoflurane
Induction characteristics	+ +	+	+	0	+ + +
Haemodynamic stability	+	+ +	+ +	+ +	+ + +
Respiratory irritation	+ + +	+ +	+ +	+	+ + +
Ease of titration	0	+	+	+ + +	+ +
Emergence characteristics	0	+ +	+	+ + +	+ +
Postoperative side effects	+	+ +	+	+ +	+ +
Potential toxicity/metabolism	0	+	+ +	+ + +	+
Cost (at low flow)	+ + +	+ +	+ +	+ +	+

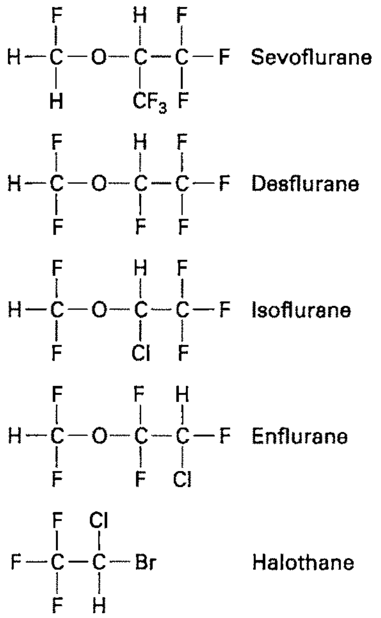


Figure 1 Chemical structure of sevoflurane compared with the other available volatile anaesthetic agents.

that of isoflurane (1.43) and compares favourably with the blood:gas solubility of both desflurane (0.42) and nitrous oxide (0.44). The low blood:gas solubility of sevoflurane should provide for rapid induction of, and recovery from, anaesthesia.

The minimum alveolar concentration (MAC) of sevoflurane is reported to be between 1.71 % [43] and 2.05 % [73]. This value was reduced to 0.66 % in an adult population by addition of approximately 60 % nitrous oxide [43]. The MAC value of sevoflurane, and therefore the typical maintenance concentration, is almost identical to that of enflurane. The MAC for sevoflurane, in common with other anaesthetics, is somewhat higher in children. Typical values are 2.6 % (reduced to 2.0 % by nitrous oxide) in children and 3.3 % in neonates [51].

Clinical properties of sevoflurane

INDUCTION OF ANAESTHESIA

While it is unlikely that inhalation induction of anaesthesia will replace the use of rapid-acting i.v. induction agents, insertion of an i.v. needle (or cannula), and even injection of i.v. anaesthetics (e.g. methohexitone, etomidate, propofol), may cause considerable discomfort, especially in children. While the use of local anaesthetics can reduce this discomfort, poor veins and a lack of co-operation can make i.v. induction of anaesthesia impractical for many patients. Induction of anaesthesia by mask may be preferable in some of these patients, assuming that this could be accomplished rapidly and smoothly. Finally, inhalation induction may be desirable on those occasions when there is a danger of airway obstruction following rapid loss of consciousness.

Anaesthetic vapours with a low blood:gas solubility coefficient should permit rapid induction of anaesthesia as the alveolar concentration equilibrates rapidly with the inspired (delivered) concentration. Based on solubility characteristics, inhalation induction should take longest with halothane, and become increasingly more rapid with enflurane, isoflurane, sevoflurane and desflurane, respectively. However, the ability to deliver an inspired concentration sufficiently high to induce anaesthesia is limited by the effects of the anaesthetic vapour on the patient's airway. In practice, agents such as enflurane, isoflurane and desflurane are irritating to the airway, resulting in coughing, breath-holding, excessive salivation and even laryngospasm. As a result, the rate of equilibration is reduced and induction is slower than would be predicted from the blood:gas solubility value alone. For example, inhalation induction with desflurane resulted in airway complications in 30–40 % of healthy, day-case patients, with occasional prolonged or failed inductions [82], while desflurane appears to be even more irritant in children, with up to 58 % of cases coughing [92].

In contrast, sevoflurane is pleasant-smelling and relatively non-irritating to the airways, permitting a high inspired concentration to be inhaled without side effects or discomfort. When a group of unpremedicated patients undergoing major gynaecological surgery were allowed to breathe 5 % sevoflurane in an oxygen–nitrous oxide mixture, anaesthesia was induced within 109 ± 25 s [76]. Anaesthesia was induced successfully in all 25 patients, none of whom coughed, experienced apnoea, laryngospasm or other airway-related side effects. Yurino and Kimura studied a group of unpremedicated volunteers in whom anaesthesia was induced by breathing oxygen–nitrous oxide to which sevoflurane was added, beginning at 0.5 % and increasing to a maximum of 4.5 % in increments of 0.5 % every 3–4 breaths [90]. Using this traditional (stepwise) technique, anaesthesia was induced in 108 ± 19 s. Laryngospasm and breath-holding were not observed, and while coughing occurred in 12.5 % of subjects, this was described as "mild" and did not adversely affect haemoglobin oxygen saturation [90]. When 4.5 %

sevoflurane was administered to a similar group of volunteers as a single, vital capacity breath, loss of consciousness was achieved in only 54 ± 10 s, while the incidence of coughing was reduced to 6.3 % [90]. Compared with isoflurane, vital capacity single breath induction with 1.7 MAC of sevoflurane was more rapid (120 ± 24 *vs* 145 ± 39 s) and associated with significantly fewer respiratory complications [89]. For example, coughing occurred in 43 % of patients breathing isoflurane compared with none with sevoflurane. In addition, one patient (4.8 %) in the isoflurane group developed laryngospasm, and the technique was abandoned in another patient because of excessive involuntary movements [89]. The majority of patients (60 %) found sevoflurane to be "pleasant smelling", while 75 % found isoflurane "unpleasant" [89]. The use of even higher concentrations of sevoflurane (up to 8 % on the newest vaporizers) permits even more rapid induction of anaesthesia. Using 7.5 % sevoflurane as a single vital capacity breath allowed loss of consciousness in 41 ± 16 s [91]. However, coughing was more common (25 %) when 7.5 % sevoflurane was used in a tidal breathing induction technique, resulting in slower induction of anaesthesia (52 ± 13 s) [91].

Inhalation induction is practised more commonly in children than in adults, and halothane has been considered the drug of choice. Early clinical experience from Japan suggested that inhalation induction with sevoflurane was "smoother" compared with halothane in children [61]. Most early investigations have reported inhalation induction times in children to be similar, irrespective of whether sevoflurane or halothane were administered [63, 67]. However, in at least one investigation, the average concentration of halothane administered was considerably higher (in terms of MAC-multiples) compared with sevoflurane, which may have distorted the results obtained [63]. Lerman and colleagues achieved an average time to loss of the eyelash reflex of 54 s in infants (< 1 yr) and 73–80 s in children aged 3–12 yr when a traditional induction sequence was used in a non-comparative evaluation [51]. Sevoflurane was administered in oxygen, commencing at 1.5 %, and increased by 1.5 % every 3 breaths. Premedication was not administered, and the incidence of airway-related complications was very low in all age groups [51]. Continuing the induction sequence, tracheal intubation was possible with deep sevoflurane anaesthesia after 4–5 min [51]. Smooth and uneventful tracheal intubation requires a sevoflurane concentration approximately 33 % above the MAC value [39]. However, insertion of the less stimulating laryngeal mask airway is possible at 1 MAC of sevoflurane [80].

Recent investigations in the paediatric population have demonstrated more rapid induction of anaesthesia with sevoflurane compared with halothane [1, 20, 32, 81]. For example, children receiving a stepwise induction technique lost their eyelash reflex in 1.7 min with sevoflurane compared with 2.2 min with halothane ($P < 0.001$) [1]. Similarly, Epstein and colleagues completed induction of anaesthesia in children in 97 ± 31 s using sevoflurane compared with 120 ± 36 s with halothane ($P < 0.05$) [20]. Even more rapid induction was reported in children aged 1–12 yr by Greenspun and co-workers [32]. Loss of the eyelash reflex occurred in 1.0 ± 0.2 min with sevoflurane compared with 1.4 ± 0.4 min with halothane ($P = 0.0002$), using a similar induction technique to the two previous studies [32]. Taivainen and colleagues also achieved induction times of 1 min with sevoflurane, administering concentrations up to 7 % [81]. Significantly more children rated their induction with sevoflurane as "pleasant" compared with halothane (56 % *vs* 20 %) and expressed a preference for a similar technique in the future (76 % *vs* 44 %) [81]. Although Sarner and colleagues did not detect any difference in induction times when comparing sevoflurane in oxygen with sevoflurane–nitrous oxide and halothane–nitrous oxide, omission of nitrous oxide increased the incidence of excitatory activity on induction with 5–35 % sevoflurane [72].

Therefore, sevoflurane appears to be a practical and well-tolerated inhalation induction agent in all age groups investigated to date. In children, it will challenge halothane as the inhalation induction agent of choice. Although the use of sevoflurane for inhalation induction in adults is likely to be more limited, it provides a viable alternative to i.v. induction techniques. Before sevoflurane can be recommended for use in association with the "difficult airway", its safety in partial airway obstruction and in patients with irritable airways needs to be investigated.

MAINTENANCE OF ANAESTHESIA

Anaesthetists are familiar with the titration of volatile agents to maintain an appropriate "depth" of anaesthesia. The rapidity with which alteration in the anaesthetic vaporizer dial setting results in a change in the level of anaesthesia is determined by the difference between the anaesthetic concentration delivered by the vaporizer and the concentration in the CNS [18]. The ratio of these two concentrations is influenced by the extent of rebreathing, which in turn depends on the type of anaesthetic circuit and the total fresh gas flow, in addition to anaesthetic uptake from the alveoli. For a given degree of rebreathing, the less soluble volatile agents allow for more rapid and precise control of anaesthetic depth, as their uptake from the alveoli is less than for agents with a higher blood:gas solubility. Although large alterations in the administered anaesthetic concentration may induce airway irritation in lightly anaesthetized, spontaneously breathing patients, this is rarely a problem after i.v. induction of anaesthesia or when neuromuscular blockers and controlled ventilation are used.

As the ratio between the delivered and alveolar concentration of sevoflurane is four times less than that achieved with isoflurane at a given fresh gas flow, greater precision in the control of anaesthetic depth should be achieved with this new agent [18]. Because it is even less soluble than sevoflurane, desflurane results in a delivered:alveolar concentration difference that is five times smaller than isoflurane. However, rapid increases in the delivered concentration of desflurane can induce transient increases in heart rate, arterial pressure, or both [16, 85]. While these changes do not appear to pose a significant hazard to most patients, the phenomenon may deter anaesthetists from adjusting the depth of anaesthesia as rapidly as the physical properties of desflurane would allow in patients with pre-existing cardiovascular disease. In contrast, these excitatory phenomena are not observed when the level of sevoflurane anaesthesia is adjusted rapidly [16].

The pharmacodynamic effects of sevoflurane on the various organ systems appear to be similar to those of other commonly used halogenated ethers. Sevoflurane produces dose-dependent ventilatory depression [14] and also reduces respiratory drive in response to hypoxia and increases in carbon dioxide partial pressure, comparable with levels achieved with other ether anaesthetics. It relaxes bronchial smooth muscle, although perhaps not as effectively as halothane. Sevoflurane decreases mean arterial pressure predominantly through decreased peripheral resistance, with cardiac output being well maintained over the normal anaesthetic maintenance range. A degree of myocardial depression occurs at higher concentrations, as a result of an effect on calcium channels [33]. Sevoflurane does not sensitize the myocardium to the arrhythmogenic effects of catecholamines [65]. Sevoflurane has little effect on normal myocardial blood flow, is a less potent coronary arteriolar dilator than isoflurane [35], and does not appear to cause "coronary steal" [44]. In contrast with other halogenated ethers, sevoflurane appears to be associated with a lower heart rate [16, 26], which helps to reduce myocardial oxygen consumption and assists myocardial perfusion. In addition, the lack of an anaesthetic-specific increase in heart rate may facilitate the determination of "depth of anaesthesia".

Sevoflurane has CNS effects similar to those of isoflurane and desflurane. Intracranial pressure increases at high inspired concentrations of sevoflurane (analogous to isoflurane); however, this effect is minimal over the 0.5–1-MAC range [74]. Sevoflurane is not associated with convulsive or epileptic activity [74]. Renal and hepatic blood flow are well preserved with sevoflurane, and organ toxicity has not been observed to date. There are limited data on sevoflurane in the obstetric population [30]. However, sevoflurane appears to have similar uterine effects to isoflurane, and no differences in maternal or fetal outcome were observed when equianaesthetic concentrations (0.5 MAC) of these two agents were compared during elective Caesarean section [30]. Sevoflurane produces clinically useful neuromuscular block and potentiates neuromuscular blockers to a similar degree to other anaesthetics. It can trigger malignant hyperpyrexia in susceptible individuals, and at least four cases have been reported to date [15].

EMERGENCE AND RECOVERY CHARACTERISTICS

The low blood:gas solubility of sevoflurane should permit rapid elimination from the CNS. When sevoflurane and isoflurane were compared as anaesthetic maintenance agents after induction of anaesthesia with midazolam and thiopentone in healthy patients undergoing elective operations, the average times from end of anaesthesia to eye opening on command were 18.6 ± 2.0 min for isoflurane and 7.5 ± 0.5 min for sevoflurane ($P < 0.001$) [26]. When propofol was used as the induction agent before operations lasting approximately 2.5 h, emergence from sevoflurane–nitrous oxide anaesthesia (4.1 ± 2.2 min) was still significantly more rapid compared with isoflurane–nitrous oxide (6.7 ± 2.2 min) [76].

Recovery from the newer volatile anaesthetic agents appears relatively unaffected by the duration of anaesthetic exposure, whereas recovery from more soluble agents increases in direct proportion to the length of anaesthetic administration [19]. While emergence times from sevoflurane remained reasonably constant over a range of anaesthetic durations from 1–7 MAC-h in healthy patients undergoing elective surgery, emergence times from isoflurane demonstrated a five-fold difference over a similar range of exposure times [26]. Nevertheless, Quinn and colleagues failed to detect any difference in emergence times between sevoflurane and isoflurane after operations lasting 3 h [68]. However, sevoflurane was associated with faster emergence compared with isoflurane using a similar technique for gynaecological operations of shorter duration, suggesting that the use of intraoperative opioid analgesics may have masked differences between the two groups in the former study, which also involved very small numbers of patients [68].

Rapidly eliminated anaesthetic agents are used most commonly for day-case anaesthesia, where rapid, clear-headed recovery may allow for earlier discharge of patients. In a randomized (non-blinded) investigation, Fredman and colleagues [23] compared a variable rate continuous infusion of propofol with sevoflurane for maintenance of anaesthesia in combination with nitrous oxide after induction of anaesthesia with propofol in a group of patients undergoing day-case gynaecological or ENT operations. The investigation also included a third group of patients who received sevoflurane–nitrous oxide for both induction and maintenance of anaesthesia. There were no significant differences in early or intermediate recovery times between the three treatment groups (table 2). Pencil and paper tests also failed to detect any significant differences between the three treatment groups in terms of postoperative sedation or psychomotor impairment [23]. In a similar investigation during day-case surgery procedures lasting approximately 90 min, emergence from sevoflurane anaesthesia required 10.4 ± 6.5 min compared with 11.0 ± 11.0 min after propofol anaesthesia [38]. In common with the study of Fredman and colleagues [23], both groups of patients received propofol for induction and nitrous oxide for maintenance of anaesthesia [38].

When sevoflurane was compared with desflurane for maintenance of anaesthesia in a group of women undergoing day-case laparoscopic sterilization, mean time to eye opening after desflurane (4.8 (SD 2.4) min) occurred significantly earlier compared with sevo-

Table 2 Recovery times (mean (SD)) for the three different anaesthetic techniques after day-case anaesthesia (propofol–propofol/nitrous oxide (N_2O), propofol–sevoflurane/nitrous oxide and sevoflurane/nitrous oxide). Adapted from Fredman and colleagues [23], with permission

	Propofol: propofol–N_2O	Propofol: sevoflurane–N_2O	Sevoflurane–N_2O: sevoflurane–N_2O
Number (*n*)	50	48	48
Anaesthesia time (min)	74 (29)	78 (28)	82 (26)
Eye opening (min)	9 (4)	9 (5)	10 (5)
Extubation (min)	10 (5)	11 (6)	11 (6)
Verbal commands (min)	11 (5)	12 (7)	12 (6)
Orientation (min)	13 (7)	13 (7)	15 (10)
Ambulation (min)	146 (71)	156 (73)	165 (67)
Fit for discharge (min)	183 (82)	184 (82)	207 (65)
Future preference (%)	98	96	97

Table 3 Comparison of emergence and recovery times (mean (SD)) in day-case patients undergoing gynaecological laparoscopies with a propofol–sevoflurane/nitrous oxide (N_2O) or a propofol–desflurane/nitrous oxide technique. * $P < 0.05$ compared with sevoflurane group. Adapted from Nathanson and colleagues [64], with permission

	Propofol: sevoflurane–N_2O	Propofol: desflurane–N_2O
Number (*n*)	21	21
Anaesthesia time (min)	79 (17)	92 (31)
Eye opening (min)	7.8 (3.8)	4.8 (2.4)*
Extubation (min)	8.2 (3.2)	5.1 (3.2)*
Obey commands (min)	10.2 (5.3)	6.4 (4.7)
Orientation (min)	11.2 (5.1)	9.3 (5.1)
Transfer to phase II recovery (min)	41 (11)	51 (20)
Ambulation (min)	124 (37)	126 (36)
Discharge (min)	193 (54)	201 (90)

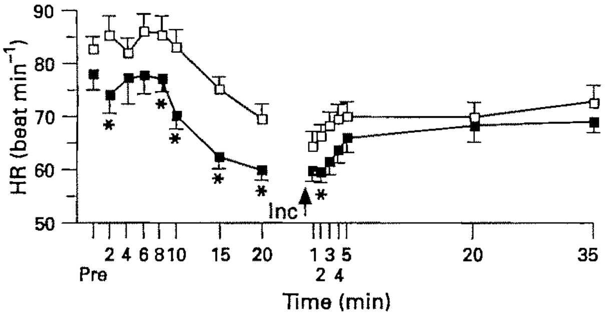


Figure 2 Heart rate (HR) values (mean, SEM) before anaesthesia (Pre) and after induction of anaesthesia and skin incision (Inc), in patients anaesthetized with propofol–desflurane–nitrous oxide (□) or propofol–sevoflurane–nitrous oxide (■). * $P < 0.05$ compared with desflurane group. Modified from Nathanson and colleagues [64], with permission.

flurane (7.8 (3.8) min) (table 3) [64]. In this preliminary investigation, anaesthesia was induced with propofol and fentanyl, and the volatile anaesthetic agents were titrated to maintain haemodynamic stability in an attempt to ensure comparable levels of anaesthesia (fig. 2) [64]. Despite more rapid emergence from desflurane anaesthesia, subsequent recovery end-points (e.g. orientation, ambulation and hospital discharge) did not differ between the two anaesthetic groups. There were also no differences in subjective feelings or psychomotor function during the recovery period, suggesting that any differences between these two anaesthetic agents are of minimal clinical significance when used for day-case anaesthesia [64].

Sevoflurane and desflurane have also been compared as anaesthetic maintenance agents in children [86]. In this study, anaesthesia was induced in both groups with halothane, which was then discontinued and the maintenance anaesthetic introduced. In common with the findings of Nathanson and colleagues, [64] in adults, emergence was delayed in children anaesthetized with sevoflurane compared with desflurane. However, the more rapid emergence after desflurane (5 ± 2 min *vs* 11 ± 4 min) was associated with a significantly higher incidence (55 %) of agitation and excitement in these children [86]. Although early recovery was also delayed after sevoflurane (19 ± 7 min *vs* 11 ± 4 min for desflurane), later recovery events were similar after both maintenance anaesthetics [86].

When halothane is used for induction of anaesthesia in children, it is often used subsequently as the anaesthetic maintenance agent. In comparison with halothane, the use of sevoflurane for induction and maintenance of anaesthesia permitted significantly more rapid eye opening (4.3 ± 1.1 *vs* 9.5 ± 2.7 min) after the end of anaesthesia [63]. The difference in recovery times persisted throughout the postoperative period, and allowed the children who had received sevoflurane to be discharged home almost 50 min earlier than those exposed to halothane (88 ± 23 *vs* 137 ± 21 min, respectively) [63]. The postoperative effects of halothane may be prolonged. In one group of paediatric inpatients, psychomotor performance on the Trieger dot test was significantly better for at least 6 h after sevoflurane anaesthesia compared with halothane [81]. Epstein and colleagues reported significantly faster emergence from sevoflurane anaesthesia compared with halothane (9.9 ± 2.9 min *vs* 12.5 ± 4.7 min), despite a higher MAC-multiple of sevoflurane concentration at the end of anaesthesia [20]. Similar findings were observed in another group of children undergoing minor surgical procedures with halothane or sevoflurane anaesthesia [67]. Tracheal extubation was possible 5 min earlier in children anaesthetized with sevoflurane compared with halothane ($P < 0.01$), while response to commands occurred 15 min earlier after sevoflurane [67]. However, a rigid hospital procedure prevented differences in discharge times from being detected in this investigation [67]. After ENT operations, discharge times did not differ following sevoflurane or halothane anaesthesia, despite more rapid awakening and early recovery with sevoflurane [32]. However, the requirements for postoperative opioid analgesia may have masked differences between the groups, while hospital discharge may also have been delayed by a relatively high incidence of postoperative vomiting in both groups of children [32]. In contrast, another clinical investigation demonstrated earlier hospital discharge after anaesthesia with sevoflurane compared with halothane, despite similar emergence times with both agents [72].

Metabolism and toxicity

In contrast with other recently introduced volatile anaesthetics, sevoflurane is a comparatively unstable molecule. It undergoes a moderate degree of metabolism (approximately 5 %) [6] and also breaks down in the presence of soda lime and Baralyme at elevated temperatures [79]. Both processes result in potentially toxic products. However, unlike other anaesthetic ethers, sevoflurane does not possess a CF_2H group, and so (similar to halothane) does not result in the production of carbon monoxide in association with excessively dry carbon dioxide absorbants [22].

Sevoflurane is metabolized by the liver to produce hexafluoroisopropanol and inorganic fluoride ions [24, 37, 50]. In humans, up to 5 % of the administered dose of sevoflurane undergoes metabolism [48, 75], catalysed by the 2E1 isoform of cytochrome P450 [45, 49]. Studies in animals have demonstrated that this enzyme can be induced by phenobarbitone [11, 54], isoniazid [69] and ethanol [55], leading to increased serum inorganic fluoride concentration and urinary excretion of fluoride ions.

RENAL EFFECTS

Clinical experience with methoxyflurane suggested that renal impairment could occur if a "threshold" serum fluoride concentration of 50 μmol litre^{-1} was exceeded [13], although clinically evident renal dysfunction was rarely observed at concentrations less than 80 μmol litre^{-1} [58]. After administration of sevoflurane anaesthesia for 1 h, Holaday and Smith found a mean serum fluoride concentration of 22 μmol litre^{-1} in six volunteers [37]. Smith, Ding and White measured serum fluoride concentrations in 50 patients receiving sevoflurane anaesthesia for gynaecological surgery of 135 min mean duration [76]. Fluoride concentrations increased rapidly after exposure to sevoflurane (fig 3), and reached a mean concentration of 25 μmol litre^{-1} at the end of operation. Frink and colleagues reported a mean peak plasma fluoride concentration of 29.3 μmol litre^{-1} 2 h after the end of surgical anaesthesia with 1–7 MAC-h of sevoflurane [24]. Similarly, Newman and colleagues found a mean peak fluoride ion concentration of less than 25 μmol litre^{-1} after 50–350 min of sevoflurane anaesthesia (mean exposure 0.8 MAC-h) in 25 patients [66]. The highest individual fluoride concentration recorded in this investigation was 40.4 μmol litre^{-1} [66]. Unlike other fluoride-producing volatile anaesthetics (e.g. methoxyflurane, halothane, enflurane), fluoride concentrations in morbidly obese patients exposed to sevoflurane were no higher than those detected in patients of normal weight [27].

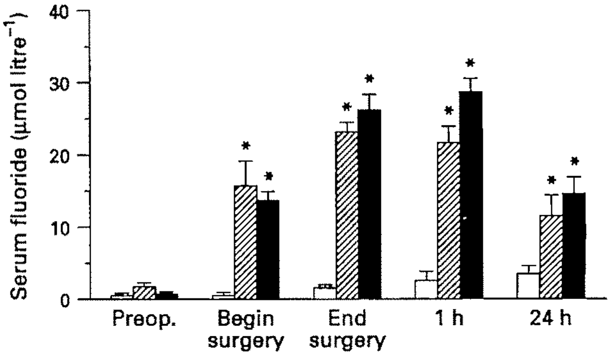


Figure 3 Concentrations of serum fluoride ions (mean, SEM) detected before induction of anaesthesia (Preop.), 30 min after induction (Begin surgery), immediately after the end of anaesthesia (End surgery), and 1 h and 24 h after operation in the propofol–isoflurane (□), propofol–sevoflurane (▨) and sevoflurane–sevoflurane (■) groups. $*P < 0.05$ compared with propofol–isoflurane group. Modified from Smith, Ding and White [76], with permission.

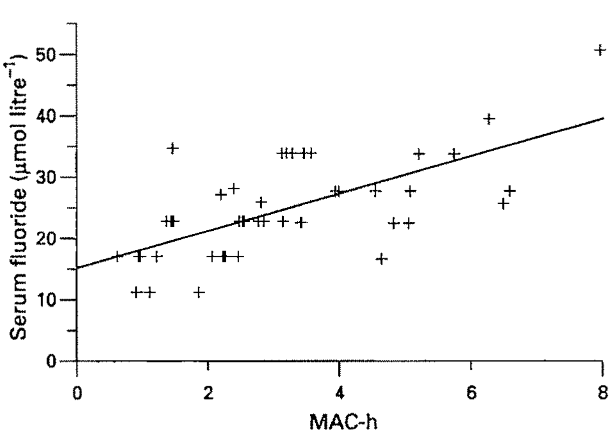


Figure 4 Correlation between serum fluoride ions measured immediately after discontinuation of anaesthesia and anaesthetic exposure in MAC-h for patients receiving sevoflurane for maintenance of anaesthesia ($r^2 = 0.45$). Modified from Smith, Ding and White [76], with permission.

A positive correlation has been demonstrated between peak concentrations of fluoride ions and duration of exposure to sevoflurane (fig. 4). After 1.1 MAC-h of sevoflurane, Shiraishi and Ikeda found that the mean peak serum inorganic fluoride concentration was only 19.3 μmol litre^{-1} [75]. In another study, plasma concentrations of inorganic fluoride were less than 50 μmol litre^{-1} in all patients receiving less than 2 MAC-h of sevoflurane, whereas peak plasma concentrations exceeded 50 μmol litre^{-1} in five patients receiving an average of 4.7 MAC-h [24]. Smith, Ding and White reported a plasma fluoride concentration of 51.4 μmol litre^{-1} after 7.9 MAC-h of sevoflurane [76]. The peak concentration of inorganic fluoride after sevoflurane is similar to that after enflurane anaesthesia [57]. In a volunteer study comparing the effects of prolonged anaesthesia with sevoflurane or enflurane on renal concentration

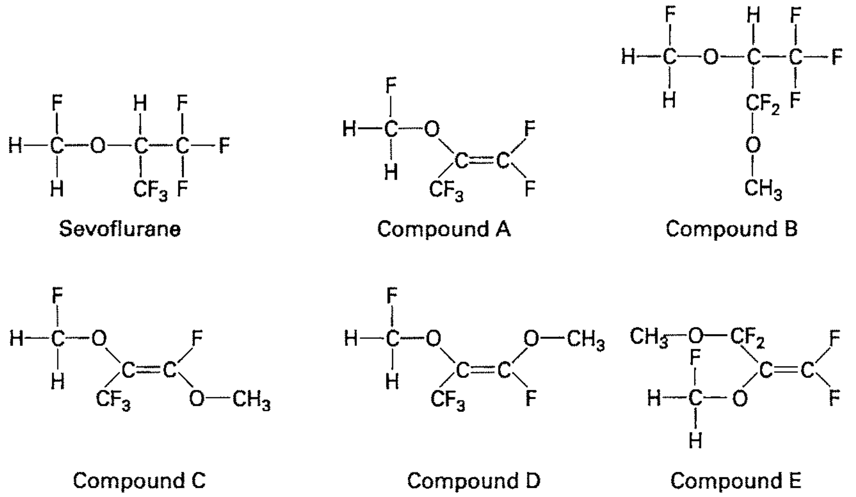


Figure 5 Degradation products of sevoflurane in soda lime under experimental conditions (⩾ 65 °C).

function, the mean peak plasma inorganic fluoride concentration was 47 μmol litre^{-1} after more than 9 MAC-h of sevoflurane anaesthesia [28]. Although three of the seven volunteers had a peak plasma fluoride concentration in excess of 50 μmol litre^{-1}, there was no demonstrable impairment of renal concentrating ability in the sevoflurane group [28]. In contrast, two of the seven volunteers in the enflurane group had reduced maximal urinary osmolality in response to desmopressin (compared with their pre-anaesthesia values) despite a mean peak plasma inorganic fluoride concentration of only 23 μmol litre^{-1} [28]. In another volunteer study involving prolonged anaesthesia, higher peak serum fluoride ions were achieved after 3, 6 and 9 MAC-h of sevoflurane than after similar durations of exposure to enflurane [62]. However, the area under the fluoride concentration–time curves was similar for comparable exposures to either anaesthetic (because of the lower solubility of sevoflurane), and no volunteer demonstrated any impairment of urine concentrating ability [62].

No alterations in urinary enzymes or postoperative renal function were detected after sevoflurane anaesthesia (0.8–2 %) lasting 9–10 h, despite a mean peak serum fluoride concentration in excess of 50 μmol litre^{-1} [56]. In a small ($n = 8$) group of patients exposed to prolonged sevoflurane anaesthesia and in whom peak serum fluoride concentration exceeded 50 μmol litre^{-1}, a slight reduction in urine concentrating ability in response to vasopressin was observed compared with a similar group of patients anaesthetized with isoflurane [34]. However, this difference was not statistically significant and, in addition, patients anaesthetized with sevoflurane had also received more perioperative fluid, which may have affected urine concentrating ability [34]. The nephrotoxic effects of sevoflurane and enflurane have recently been compared in patients with chronically impaired renal function, defined as a serum creatinine concentration of ⩾ 1.5 mg dl^{-1} (130 μmol litre^{-1}) [10]. Sevoflurane and enflurane resulted in peak serum fluoride concentrations of 25 and 13 μmol litre^{-1}, respectively, but neither agent resulted in alterations in postoperative laboratory tests of renal function or in deterioration in renal function [10]. Similar findings were obtained in another preliminary investigation in patients with renal insufficiency (serum creatinine 130–260 μmol litre^{-1}), in whom 0.8–6.5 MAC-h of sevoflurane anaesthesia did not alter serum creatinine or creatinine clearance [53].

It would appear that renal toxicity is not an inevitable consequence of exceeding a "threshold" serum concentration of fluoride ions. Indeed, we must be careful to avoid "applying a fluoride hypothesis developed to explain methoxyflurane nephrotoxicity non-selectively to all anesthetics without supporting data" [47]. The apparent lack of renal toxicity with sevoflurane in humans may be related to its relative insolubility and site of metabolism. Although the rate of *in vitro* hepatic microsomal metabolism of sevoflurane may be similar to that of methoxyflurane, the rapid elimination of sevoflurane reduces the total amount of drug available for *in vivo* metabolism [12], resulting in a rapid decrease in organic fluoride concentration after sevoflurane administration, and probably preventing exposure to fluoride ions for a long enough duration to lead to clinically detectable toxicity [24]. Recent evidence from Kharasch, Hankins and Thummel [46] suggested that intrarenal production of fluoride ions may be more important in the aetiology of methoxyflurane-induced toxicity than peak serum fluoride concentrations [7].

HEPATIC EFFECTS

The other major breakdown product of sevoflurane metabolism is hexafluoroisopropanol, an organic fluoride molecule which is excreted in the urine as a glucuronide conjugate [37, 41, 54]. Although this molecule is potentially hepatotoxic, conjugation of hexafluoroisopropanol occurs so rapidly [48] that clinically significant liver damage seems theoretically impossible [8]. Although the production of both inorganic fluoride ions and hexafluoroisopropanol can be reduced substantially by the selective cytochrome P450 2E1 inhibitor, disulfiram [45], this is unlikely to be a necessary clinical strategy.

INTERACTION WITH CARBON DIOXIDE ABSORBANTS

Another concern with sevoflurane is its interaction with carbon dioxide absorbants. Sevoflurane is absorbed and degraded by both soda lime and Baralyme [2, 29, 52, 79, 84, 87]. When sevoflurane is mixed with soda lime, sealed in a flask and heated, a total of five breakdown products are produced (fig. 5). These have been designated as compounds A, B, C, D and E [8]. However, only compound A (and to a lesser extent compound B) is produced under conditions likely to be encountered clinically. Concern has been raised because these products are toxic in rats. Morio and colleagues determined that the concentration of compound A required to kill 50% of rats (LC_{50}) after 1 h exposure was 1090 ppm and 1050 ppm for males and females, respectively [59]. The LC_{50} for compound A was reduced to approximately 400 ppm after 3 h exposure [31, 59]. The toxicity produced by compound A in rats primarily involves renal, hepatic and cerebral damage.

If it is assumed that compound A produces similarly toxicity in humans, are patients likely to be at significant risk if sevoflurane is delivered from a circle absorber breathing circuit? The evidence suggests that the concentration of compound A achieved in clinical practice is well below the concentration which is toxic to animals. Bito and Ikeda exposed patients to similar concentrations of sevoflurane at various fresh gas flows [3]. Compound A was the only sevoflurane degradation product detected at any of the three fresh gas flow rates examined. The mean maximal concentrations of compound A detected were 19.7 ± 4.3, 8.1 ± 2.7 and 2.1 ± 1.0 ppm at 1, 3 and 6 litre min^{-1}, respectively [3]. The concentration of compound A remained relatively constant between 1 and 3 h of exposure to sevoflurane at all three flow rates [3]. Frink and colleagues examined sevoflurane degradation products during low-flow (770 ml min^{-1}) anaesthesia using either soda lime or Baralyme as the absorbent [29]. All patients received an anaesthetic concentration of sevoflurane for at least 3 h. As in the previous study, compound A was the only breakdown product detected within the circle system. The mean maximal concentration of compound A was 8.2 ± 2.7 ppm when soda lime was used as the absorbant and 20.3 ± 8.7 ppm with Baralyme [29]. The highest concentration of compound A detected in any individual patient was 15.2 ppm with soda lime and 60.8 ppm with Baralyme [29]. Concentrations of compound A increased progressively over the first 4 h of anaesthesia and then declined with continuing exposure to sevoflurane [29]. Similar findings were obtained in another study using even lower gas flows (350 ml min^{-1}) in association with soda lime, in which 17 patients received an average of 2.3 MAC-h of sevoflurane [88]. The mean concentration of compound A was found to be 6 ppm, and the highest recorded value was 22 ppm [88]. After more prolonged exposure, the mean maximum concentration of compound A was 7.6 ± 1.0 ppm, with the highest individual value of 14.1 ppm occurring after 5 h exposure to sevoflurane at a flow of 5 litre min^{-1} [40]. Even after 9 h exposure to 1–1.2 MAC of sevoflurane anaesthesia at 5 litre min^{-1} in volunteers, peak compound A concentrations averaged only 7.6 ± 1.0 ppm, with the maximal concentration occurring after 2 h and remaining constant or declining thereafter [25]. During prolonged exposure (up to 18 h) at low fresh gas flows (1 litre min^{-1}), the mean peak concentrations of compound A achieved were 23.6 ppm and 32.0 ppm using soda lime and Baralyme, respectively [4]. The highest concentration of compound A detected in any patient was 37.4 ppm when soda lime was used as the absorbant, and 41.2 ppm with Baralyme. Compound A concentrations peaked in the first 2–4 h, remained relatively constant from 4–10 h and then declined with continuing anaesthesia [4]. Compound B was detected in small quantities ($\leqslant 0.2$ ppm) in two of the patients in the Baralyme group, but was not found when soda lime was used as the absorbant for prolonged anaesthesia [4].

In a totally closed system, a mean concentration of 19.5 ± 5.4 ppm of compound A was detected after 1 h [2]. The concentration of compound A remained relatively constant over the next 4 h and subsequently decreased slightly with continuing sevoflurane anaesthesia. The highest concentration detected in any patient was 30 ppm [2]. Compound B was also detected in 70% of patients during closed circuit anaesthesia, although the concentration did not exceed 1.5 ppm in any patient [2].

Degradation of sevoflurane appears to be temperature-dependent [59, 79, 87]. The higher concentration of compound A which is produced by interaction with Baralyme probably occurs as a consequence of the higher temperature attained in this absorbant compared with soda lime [29]. Similarly, increased minute ventilation and greater carbon dioxide production both increase absorbant temperature, and hence production of compound A [21]. Chilling soda lime by immersing the carbon dioxide absorbant canister into an ice bath prevented formation of compounds B, C and D and significantly reduced the formation of compound A in a model lung [70]. The production of compound A by interaction with Baralyme is reduced by the presence of water, and also decreases as Baralyme becomes exhausted [87]. These factors may also limit sevoflurane breakdown in clinical practice. Finally, the concentration of compound A is highest during low-flow anaesthesia, and decreased by increasing fresh gas flow [3]. The use of higher flow rates probably increases the washout of breakdown products, while reducing rebreathing and producing lower absorbant temperatures [18].

The amount of compound A produced under a variety of clinically relevant circumstances has always been substantially lower than that which produces acute toxicity in animals. Compound B is somewhat less toxic than compound A [59], and is formed only in a totally closed anaesthetic breathing system or after prolonged anaesthesia at very low flows. However, the concentration recorded is orders of magnitude below the toxic concentration. A further concern has been raised recently because of the finding that exposure of rats to compound A at concentrations of > 50 ppm results in renal corticomedullary tubular necrosis [31]. Clearly, this concentration is much closer to that which has been achieved clinically. However, the natural history and clinical relevance of these histological findings are unknown, as all rats in this study were killed within 4 days of exposure to compound A. Indeed, the renal damage appeared to be less extensive 4 days after exposure to compound A than on the first day, suggesting that the lesions were at least partially reversible [31]. Furthermore, it should also be mentioned that the objectivity of this investigation has been questioned by the editor of the journal in which the article was published [71]. A follow-up study by the same investigative group showed that renal injury in rats required at least 200 ppm when exposure to compound A was limited to 1 h [42]. It is not known whether compound A has a similar pattern of toxicity in humans [17].

Sevoflurane has now been administered to about 1 million patients in Japan without reports of serious adverse reactions or significant hepatic or nephrotoxicity [9, 60]. In addition, no evidence of renal injury or impairment has been detected in any of the published studies of sevoflurane anaesthesia in humans [10, 24, 28, 50, 53, 75, 76]. The effects of multiple exposures to sevoflurane anaesthesia have been evaluated recently in primates [77]. Although subtle increases in hepatic enzymes were detected, these were less marked than the increase caused by multiple exposures to other volatile anaesthetics. No evidence of histopathological toxicity was detected after 24 exposures to 3–5 MAC-h of sevoflurane in cynomolgus monkeys [77]. Thus the toxicity of sevoflurane would appear to be more of a theoretical than a clinical problem. However, with worldwide clinical exposure to this volatile anaesthetic, any significant toxic effects should become apparent in the near future.

Conclusion

Sevoflurane is not the "ideal" volatile anaesthetic. However, its low blood:gas solubility in combination with minimal airway irritation allows for smooth and rapid induction of anaesthesia. Although these properties may be of benefit to adult patients, sevoflurane is likely to become an even more popular choice for paediatric anaesthesia. Rapid recovery compared with halothane, and smooth and calm emergence are also advantageous in children. For adults, the relative insolubility of sevoflurane should facilitate control of anaesthetic depth during the maintenance period, even at low gas flows. Combined with conventional vaporizer technology and a familiar concentration range, anaesthetists should have little difficulty in using sevoflurane as a maintenance anaesthetic. Rapid emergence from anaesthesia with sevoflurane facilitates more efficient patient turnover and may confer additional benefits after more prolonged anaesthesia.

While sevoflurane diverges from the mythical ideal anaesthetic in its degree of metabolism and potentially toxic byproducts, the body of experimental and clinical evidence to date suggests that sevoflurane is safe when administered under the usual clinical conditions. Further investigations may be required before sevoflurane can be declared safe under *all* circumstances (e.g. low-flow or closed circuit anaesthesia, in the presence of chronic renal insufficiency). For the present, it is wise to caution against the use of sevoflurane in patients with significantly impaired renal function [58] and for prolonged anaesthesia at very low total fresh gas flows (< 2 litre min^{-1}). Indeed, the USA product licence for sevoflurane contains just such restrictions, although similar limitations have not been applied in the UK.

The relative cost of sevoflurane is unknown at present. Sevoflurane can be administered safely at low gas flows (2–3 litre min^{-1}), and its low solubility will assist in adjusting its delivery. Further investigations are required to determine the most beneficial and cost effective use of sevoflurane. Nevertheless, the long-awaited arrival of this volatile agent should prove to be a most useful addition to clinical anaesthesia.

References

1. Binstock WB, Berkowitz R, Eyrich K, Hannallah RS, Apfelbaum JL. A comparison of sevoflurane and halothane for induction and maintenance of anesthesia in pediatric ASA I and II outpatients. *Anesthesiology* 1994; **81**: A1313.
2. Bito H, Ikeda K. Closed-circuit anesthesia with sevoflurane in humans. *Anesthesiology* 1994; **80**: 71–76.
3. Bito H, Ikeda K. Effect of total flow rate on the concentration of degradation products generated by reaction between sevoflurane and soda lime. *British Journal of Anaesthesia* 1995; **74**: 667–669.
4. Bito H, Ikeda K. Long-duration, low-flow sevoflurane anesthesia using two carbon dioxide absorbants. *Anesthesiology* 1995; **81**: 340–345.
5. Booth HS, Bixby EM. Fluorine derivatives of chloroform. *Industrial and Engineering Chemistry* 1932; **24**: 637–641.
6. Brown BR jr. Sevoflurane, fluoride ion, and renal toxicity—In reply. *Anesthesiology* 1995; **83**: 233–234.
7. Brown BR jr. Shibboleths and jigsaw puzzles: The fluoride nephrotoxicity enigma *Anesthesiology* 1995; **82**: 607–608.
8. Brown BR jr, Frink EJ jr. Whatever happened to sevoflurane? *Canadian Journal of Anaesthesia* 1992; **39**: 207–209.
9. Brown BR jr, Frink EJ jr. The safety of sevoflurane in humans: II. *Anesthesiology* 1993; **79**: 201–202.
10. Conzen PF, Nuscheler M, Melotte A, Verhaegen M, Leupolt T, Van Aken H, Peter K. Renal function and serum fluoride concentrations in patients with stable renal insufficiency after anesthesia with sevoflurane or enflurane. *Anesthesia and Analgesia* 1995; **81**: 569–575.
11. Cook TL, Beppu WJ, Hitt BA, Kosek JC, Mazze RI. A comparison of renal effects and metabolism of sevoflurane and methoxyflurane in enzyme-induced rats. *Anesthesia and Analgesia* 1975; **54**: 829–834.
12. Cook TL, Beppu WJ, Hitt BA, Kosek JC, Mazze RI. Renal effects and metabolism of sevoflurane in Fischer 344 rats: An in-vivo and in-vitro comparison with methoxyflurane. *Anesthesiology* 1975; **43**: 70–77.
13. Cousins MJ, Mazze RI. Methoxyflurane nephrotoxicity: A study of dose response in man. *Journal of The American Medical Association* 1973; **225**: 1611–1616.
14. Doi M, Takahashi T, Ikeda K. Respiratory effects of sevoflurane used in combination with nitrous oxide and surgical stimulation. *Journal of Clinical Anesthesia* 1994; **6**: 1–4.
15. Ducart A, Adnet P, Renaud B, Riou B, Krivosic-Horber R. Malignant hyperthermia during sevoflurane administration. *Anesthesia and Analgesia* 1995; **80**: 609–611.
16. Ebert TJ, Muzi M, Lopatka CW. Neurocirculatory responses to sevoflurane in humans. A comparison to desflurane. *Anesthesiology* 1995; **83**: 88–95.
17. Eger EI II. Is there equivalence between compound A and a synthetic olefin?—In reply. *Anesthesiology* 1994; **81**: 272–273.

18. Eger EI II. New inhaled anesthetics. *Anesthesiology* 1994; **80**: 906–922.
19. Eger EI II, Johnson BH. Rates of awakening from anesthesia with I-653, halothane, isoflurane, and sevoflurane. A test of the effect of anesthetic concentration and duration in rats. *Anesthesia and Analgesia* 1987; **66**: 977–982.
20. Epstein RH, Mendel HG, Guarnieri KM, Staudt SR, Lessin JB, Marr AT. Sevoflurane *versus* halothane for general anesthesia in pediatric patients. A comparative study of vital signs, induction, and emergence. *Journal of Clinical Anesthesia* 1995; **7**: 237–244.
21. Fang ZX, Eger EI II. Factors affecting the concentration of compound A resulting from the degradation of sevoflurane by soda lime and Baralyme® in a standard anesthetic circuit. *Anesthesia and Analgesia* 1995; **81**: 564–568.
22. Fang ZX, Eger EI II, Laster MJ, Chortkoff BS, Kandel L, Ionescu P. Carbon monoxide production from degradation of desflurane, enflurane, isoflurane, halothane, and sevoflurane by soda lime and Baralyme®. *Anesthesia and Analgesia* 1995; **80**: 1187–1193.
23. Fredman B, Nathanson MH, Smith I, Wang J, Klein K, White PF. Sevoflurane for outpatient anesthesia: A comparison with propofol. *Anesthesia and Analgesia* 1995; **81**: 823–828.
24. Frink EJ jr, Ghantous H, Malan TP, Morgan S, Fernando J, Gandolfi AJ, Brown BR. Plasma inorganic fluoride with sevoflurane anesthesia: Correlation with indices of hepatic and renal function. *Anesthesia and Analgesia* 1992; **74**: 231–235.
25. Frink EJ jr, Isner RJ, Malan TP, Morgan SE, Brown EA, Brown BR jr. Sevoflurane degradation product concentrations with soda lime during prolonged anesthesia. *Journal of Clinical Anesthesia* 1994; **6**: 239–242.
26. Frink EJ jr, Malan TP, Atlas M, Dominguez LM, DiNardo JA, Brown BR jr. Clinical comparison of sevoflurane and isoflurane in healthy patients. *Anesthesia and Analgesia* 1992; **74**: 241–245.
27. Frink EJ jr, Malan TP jr, Brown EA, Morgan S, Brown BR jr. Plasma inorganic fluoride levels with sevoflurane anesthesia in morbidly obese and nonobese patients. *Anesthesia and Analgesia* 1993; **76**: 1333–1337.
28. Frink EJ jr, Malan TP, Isner RJ, Brown EA, Morgan SE, Brown BR jr. Renal concentrating function with prolonged sevoflurane or enflurane anesthesia in volunteers. *Anesthesiology* 1994; **80**: 1019–1025.
29. Frink EJ jr, Malan TP, Morgan SE, Brown EA, Malcomson M, Brown BR jr. Quantification of the degradation products of sevoflurane in two CO_2 absorbants during low-flow anesthesia in surgical patients. *Anesthesiology* 1992; **77**: 1064–1069.
30. Gambling DR, Sharma SK, White PF, Van Beveren T, Bala AS, Gouldson R. Use of sevoflurane during elective Cesarean birth: A comparison with isoflurane and spinal anesthesia. *Anesthesia and Analgesia* 1995; **81**: 90–95.
31. Gonsowski CT, Laster MJ, Eger EI II, Ferrell LD, Kerschmann RL. Toxicity of compound A in rats. Effect of a 3-hour administration. *Anesthesiology* 1994; **80**: 556–565.
32. Greenspun JCF, Hannallah RS, Welborn LG, Norden JM. Comparison of sevoflurane and halothane anesthesia in children undergoing outpatient ear, nose, and throat surgery. *Journal of Clinical Anesthesia* 1995; **7**: 398–402.
33. Hatakeyama N, Ito Y, Momose Y. Effects of sevoflurane, isoflurane, and halothane on mechanical and electrophysiologic properties of canine myocardium. *Anesthesia and Analgesia* 1993; **76**: 1327–1332.
34. Higuchi H, Sumikura H, Sumita S, Arimura S, Takamatau F, Kanno M, Satoh T. Renal function in patients with high serum fluoride concentrations after prolonged sevoflurane anesthesia. *Anesthesiology* 1995; **83**: 449–458.
35. Hirano M, Fujigaki T, Shibata O, Sumikawa K. A comparison of coronary hemodynamics during isoflurane and sevoflurane anesthesia in dogs. *Anesthesia and Analgesia* 1995; **80**: 651–656.
36. Hitt BA, Mazze RI, Cook TL, Beppu WJ, Kosek JC. Thermoregulatory defect in rats during anesthesia. *Anesthesia and Analgesia* 1977; **56**: 9–15.
37. Holaday DA, Smith FR. Clinical characteristics and biotransformation of sevoflurane in healthy human volunteers. *Anesthesiology* 1981; **54**: 100–106.
38. Huang S, Wong CH, Yang JC, Wu W. Comparison of emergence and recovery times between sevoflurane and propofol as maintenance anesthetics in adult outpatient surgeries. *Anesthesiology* 1994; **81**: A6.
39. Inomata S, Watanabe S, Taguchi M, Okada M. End-tidal sevoflurane concentration for tracheal intubation and minimal alveolar concentration in pediatric patients. *Anesthesiology* 1994; **80**: 93–96.
40. Isner RJ, Malan TP jr, Frink EJ jr, Brown ER, Morgan SE, Brown BR jr. Quantification of inhaled compound A concentrations during prolonged sevoflurane anesthesia in volunteers. *Anesthesiology* 1993; **79**: A349.
41. Jiaxiang N, Sato N, Fujii K, Yuge O. Urinary excretion of hexafluoroisopropanol glucuronide and fluoride in patients after sevoflurane anaesthesia. *Journal of Pharmacy and Pharmacology* 1993; **45**: 67–69.
42. Kandel L, Laster MJ, Eger EI II, Kerschmann RL, Martin J. Nephrotoxicity in rats undergoing a one-hour exposure to compound A. *Anesthesia and Analgesia* 1995; **81**: 559–563.
43. Katoh T, Ikeda K. The minimum alveolar concentration (MAC) of sevoflurane in humans. *Anesthesiology* 1987; **66**: 301–303.
44. Kersten JR, Bayer AP, Pagel PS, Tessmer JP, Warltier DC. Perfusion of ischemic myocardium during anesthesia with sevoflurane. *Anesthesiology* 1994; **81**: 995–1004.
45. Kharasch ED, Armstrong AS, Gunn K, Artru A, Cox K, Karol MD. Clinical sevoflurane metabolism and disposition. II. The role of cytochrome P450 2E1 in fluoride and hexafluroisopropanol formation. *Anesthesiology* 1995; **82**: 1379–1388.
46. Kharasch ED, Hankins DC, Thummel KE. Human kidney methoxyflurane and sevoflurane metabolism. Intrarenal fluoride production as a possible mechanism of methoxyflurane nephrotoxicity. *Anesthesiology* 1995; **82**: 689–699.
47. Kharasch ED, Hankins DC, Thummel KE. Sevoflurane, fluoride ion, and renal toxicity—In reply. *Anesthesiology* 1995; **83**: 234–235.
48. Kharasch ED, Karol MD, Lanni C, Sawchuk R. Clinical sevoflurane metabolism and disposition. I. Sevoflurane and metabolite pharmacokinetics. *Anesthesiology* 1995; **82**: 1369–1378.
49. Kharasch ED, Thummel KE. Identification of cytochrome P450 2E1 as the predominant enzyme catalyzing human liver microsomal defluorination of sevoflurane, isoflurane, and methoxyflurane. *Anesthesiology* 1993; **79**: 795–807.
50. Kobayashi Y, Ochiai R, Takeda J, Sekiguchi H, Fukushima K. Serum and urinary inorganic fluoride concentrations after prolonged inhalation of sevoflurane in humans. *Anesthesia and Analgesia* 1992; **74**: 753–757.
51. Lerman J, Sikich N, Kleinman S, Yentis S. The pharmacology of sevoflurane in infants and children. *Anesthesiology* 1994; **80**: 814–824.
52. Liu J, Laster MJ, Eger EI II, Taheri S. Absorption and degradation of sevoflurane and isoflurane in a conventional anesthetic circuit. *Anesthesia and Analgesia* 1991; **72**: 785–789.
53. McGrath B, Hodgins L, Frink E, Nossaman B, Bihkazi G. The effect of sevoflurane vs isoflurane on renal function in patients with renal insufficiency. *Anesthesia and Analgesia* 1995; **80**: S312.
54. Martis L, Lynch S, Napoli MD, Woods EF. Biotransformation of sevoflurane in dogs and rats. *Anesthesia and Analgesia* 1981; **60**: 186–191.
55. Masaki E, Kondou T, Kobayashi K. Relationship between serum F^- and cytochrome P-450 after sevoflurane anesthesia in ethanol treated rats. *Anesthesiology* 1990; **73**: A396.
56. Matsumura C, Kemmotsu O, Kawano Y, Takita K, Sugimoto H, Mayumi T. Serum and urine inorganic fluoride levels following prolonged low-dose sevoflurane anesthesia combined with epidural block. *Journal of Clinical Anesthesia* 1994; **6**: 419–424.
57. Mazze RI, Calverley RK, Smith NT. Inorganic fluoride nephrotoxicity: Prolonged enflurane and halothane anesthesia in volunteers. *Anesthesiology* 1977; **46**: 265–271.
58. Mazze RI, Jamison R. Renal effects of sevoflurane. *Anesthesiology* 1995; **83**: 443–445.
59. Morio M, Fujii K, Satoh N, Imai M, Kawqakami U, Mizuno T, Kawai Y, Ogasawara Y, Tamura T, Negishi A, Kumagai Y, Kawai T. Reaction of sevoflurane and its degradation

products with soda lime: Toxicity of the byproducts. *Anesthesiology* 1992; 77: 1155–1164.

60. Morio M, Fujii K, Satoh N, Tamura T. The safety of sevoflurane in humans: I. *Anesthesiology* 1993; 79: 200–201.
61. Morisaki H, Suzuki G, Miyazawa N, Kiichi Y, Misaki T, Suzuki A. A clinical trial of sevoflurane in children for herniorrhaphy. *Journal of Anesthesia* 1988; 2: 94–97.
62. Munday IT, Stoddart PA, Jones RM, Lytle J, Cross MR. Serum fluoride concentration and urine osmolality after enflurane and sevoflurane anesthesia in male volunteers. *Anesthesia and Analgesia* 1995; 81: 353–359.
63. Naito Y, Tamai S, Shingu K, Fujimori R, Mori K. Comparison between sevoflurane and halothane for paediatric ambulatory anaethesia. *British Journal of Anaesthesia* 1991; 67: 387–389.
64. Nathanson MH, Fredman B, Smith I, White PF. Sevoflurane versus desflurane for outpatient anesthesia: A comparison of maintenance and recovery profiles. *Anesthesia and Analgesia* 1995; **81**: 11.86–11.90.
65. Navarro R, Weiskopf RB, Moore MA, Lockhart S, Eger EI II, Koblin D, Lu G, Wilson C. Humans anesthetized with sevoflurane or isoflurane have similar arrhythmic response to epinephrine. *Anesthesiology* 1994; **80**: 545–549.
66. Newman PJ, Quinn AC, Hall GM, Grounds RM. Plasma inorganic fluoride ion levels following sevoflurane anaesthesia. *British Journal of Anaesthesia* 1994; 72 (Suppl. 1): A166.
67. Piat V, Dubois M-C, Johanet S, Murat I. Induction and recovery characteristics and hemodynamic responses to sevoflurane and halothane in children. *Anesthesia and Analgesia* 1994; 79: 840–844.
68. Quinn AC, Newman PJ, Hall GM, Grounds RM. Sevoflurane anaesthesia for major intra-abdominal surgery. *Anaesthesia* 1994; 49: 567–571.
69. Rice SA, Sbordone L, Mazze RI. Metabolism by rat hepatic microsomes of fluorinated ether anesthetics following isoniazid administration. *Anesthesiology* 1980; 53: 489–493.
70. Ruzicka JA, Hidalgo JC, Tinker JH, Baker MT. Inhibition of volatile sevoflurane degradation product formation in an anesthetic circuit by a reduction in soda lime temperature. *Anesthesiology* 1994; **81**: 238–244.
71. Saidman LJ. Unresolved issues relating to peer review, industry support of research, and conflict of interest. *Anesthesiology* 1994; **80**: 491–492.
72. Sarner JB, Levine M, Davis PJ, Lerman J, Cook R, Motoyama EK. Clinical characteristics of sevoflurane in children. A comparison with halothane. *Anesthesiology* 1995; **82**: 38–46.
73. Scheller MS, Saidman LJ, Partridge BL. MAC of sevoflurane in humans and the New Zealand white rabbit. *Canadian Journal of Anaesthesia* 1988; 35: 153–156.
74. Scheller MS, Teteishi A, Drummond JC, Zornow MH. The effects of sevoflurane on cerebral blood flow, cerebral metabolic rate for oxygen, intracranial pressure, and the electroencephalogram are similar to those of isoflurane in the rabbit. *Anesthesiology* 1988; **68**: 548–551.
75. Shiraishi Y, Ikeda K. Uptake and biotransformation of sevoflurane in humans: A comparative study of sevoflurane with halothane, enflurane, and isoflurane. *Journal of Clinical Anesthesia* 1990; 2: 381–386.
76. Smith I, Ding Y, White PF. Comparison of induction, maintenance and recovery characteristics of sevoflurane–N_2O and propofol–sevoflurane–N_2O with propofol–isoflurane–N_2O. *Anesthesia and Analgesia* 1992; 74: 253–259.
77. Soma LR, Tierney WJ, Hogan GK, Satoh N. The effects of multiple administrations of sevoflurane to cynomolgus monkeys: Clinical pathologic, hematologic and pathologic study. *Anesthesia and Analgesia* 1995; **81**: 347–352.
78. Strum DP, Eger EI II. Partition coefficient for sevoflurane in human blood, saline, and olive oil. *Anesthesia and Analgesia* 1987; **66**: 654–656.
79. Strum DP, Johnson BH, Eger EI II. Stability of sevoflurane in soda lime. *Anesthesiology* 1987; **67**: 779–781.
80. Taguchi M, Watanabe S, Asakura N, Inomata S. End-tidal sevoflurane concentrations for laryngeal mask airway insertion and for tracheal intubation in children. *Anesthesiology* 1994; 81: 628–631.
81. Taivainen T, Tiainen P, Meretoja OA, Räihä L, Rosenberg PH. Comparison of the effects of sevoflurane and halothane on the quality of anaesthesia and serum glutathione transferase alpha and fluoride in paediatric patients. *British Journal of Anaesthesia* 1994; 73: 590–595.
82. Van Hemelrijck J, Smith I, White PF. Use of desflurane for outpatient anesthesia: A comparison with propofol and nitrous oxide. *Anesthesiology* 1991; 75: 197–203.
83. Wallin RF, Napoli MD. Sevoflurane (fluoro-methyl-1,1,1,3,3,3-hexafluro-2-propyl ether): a new inhalational anesthetic agent. *Federated Proceedings* 1971; **30**: 442.
84. Wallin RF, Regan BM, Napoli MD, Stern IJ. Sevoflurane: A new inhalational anesthetic agent. *Anesthesia and Analgesia* 1975; 54: 758–765.
85. Weiskopf RB, Moore MA, Eger EI II, Noorani M, McKay L, Chortkoff B, Hart PS, Damask M. Rapid increase in desflurane concentration is associated with greater transient cardiovascular stimulation than with rapid increase in isoflurane concentration in humans. *Anesthesiology* 1994; **80**: 1035–1045.
86. Welborn LG, Frazier LJ, Hannallah RS, Norden J. Comparison of emergence and recovery characteristics of sevoflurane, desflurane, and halothane in pediatric patients. *Anesthesia and Analgesia* 1995; **80**: S550.
87. Wong DT, Lerman J. Factors affecting the rate of disappearance of sevoflurane in Baralyme. *Canadian Journal of Anaesthesia* 1992; **39**: 366–369.
88. Yasuda N, Mishina J, Miyano K, Tanifuji Y, Amaki Y, Kobayashi K. Effects of sevoflurane administered using a low flow system on the liver and kidney. *Anesthesiology* 1991; **75**: A345.
89. Yurino M, Kimura H. Vital capacity breath technique for rapid anaesthetic induction: Comparison of sevoflurane and isoflurane. *Anaesthesia* 1992; **47**: 946–949.
90. Yurino M, Kimura H. Induction of anesthesia with sevoflurane, nitrous oxide, and oxygen: A comparison of spontaneous ventilation and vital capacity rapid inhalation induction (VCRII) techniques. *Anesthesia and Analgesia* 1993; **76**: 598–601.
91. Yurino M, Kimura H. A comparison of vital capacity breath and tidal breathing techniques for induction of anaesthesia with high sevoflurane concentrations in nitrous oxide and oxygen. *Anaesthesia* 1995; **50**: 308–311.
92. Zwass MS, Fisher DM, Welborn LG, Coté CJ, Davis PJ, Dinner M, Hannallah RS, Liu LMP, Sarner J, McGill WA, Alifimoff JK, Embree PB, Cook R. Induction and maintenance characteristics of anesthesia with desflurane and nitrous oxide in infants and children. *Anesthesiology* 1992; **76**: 373–378.

British Journal of Anaesthesia 1996; **76**: 446–448

SHORT COMMUNICATIONS

Effect of neuromuscular block on depth of anaesthesia as measured by the auditory evoked response

C. E. RICHMOND, A. MATSON, C. THORNTON, C. J. DORÉ AND D. E. F. NEWTON

Summary

In a double-blind, randomized, controlled, prospective study, we have investigated the effects of vecuronium and laryngoscopy on the auditory evoked response (AER) of the electroencephalogram (EEG) in 40 ASA I and II patients under steady state anaesthesia. After stable anaesthesia had been achieved with 1.0 MAC of isoflurane and nitrous oxide in oxygen, patients were allocated randomly to receive two separate doses of vecuronium 0.05 mg kg^{-1} or saline. The AER was recorded before and after each dose and then after 20-s laryngoscopy in each group to determine any changes in the early cortical components of the AER waveform (Pa and Nb). There were no statistically significant changes between the vecuronium and saline groups. However, there was a statistically significant increase in mean Pa amplitude of 36% ($P = 0.008$) and a reduction in mean Nb latency of 6% ($P = 0.05$) after laryngoscopy in both the paralysed and unparalysed groups, and these changes did not differ significantly between groups. There were correspondingly significant haemodynamic responses to laryngoscopy in both groups. We conclude that neuromuscular block with vecuronium does not affect depth of anaesthesia as measured by the AER in either stimulated or unstimulated patients. In addition, we have demonstrated clearly the arousal effect of laryngoscopy on the AER. (*Br. J. Anaesth.* 1996; **76**: 446–448)

Key words

Neuromuscular block. Neuromuscular block, vecuronium. Larynx, laryngoscopy. Monitoring, evoked potentials. Anaesthesia, depth.

Neuromuscular block was thought to decrease anaesthetic requirements in humans [1, 2], but recent investigations have not confirmed this [3, 4]. We have used the auditory evoked response (AER), which reflects the level of anaesthetic depth [5], to investigate this effect. The Pa and Nb waves from the primary auditory cortex show graded changes in amplitude and latency with increasing concentrations for a wide range of anaesthetics [5]. When a stimulus is applied to a patient during steady state anaesthesia, for example skin incision [5], Pa and Nb amplitudes increase suggesting cortical arousal. The AER therefore reflects both the level of anaesthesia and the balance between anaesthesia and stimulation in anaesthetized patients. In this study, we have examined the effect on the AER of neuromuscular block and laryngoscopy during a period after induction of anaesthesia.

Method and results

With the approval of the Harrow Research Ethics Committee, written informed consent was obtained from 40 ASA I or II patients undergoing surgery. We chose patients only if neuromuscular block and ventilation via a laryngeal mask airway were appropriate. Patients were premedicated with temazepam 10 mg orally, 1 h before operation. Before induction, full monitoring was commenced and heart rate, oxygen saturation, arterial pressure and neuromuscular block were recorded continually. The AER was monitored as described previously [6]. Anaesthesia was induced with fentanyl 1 μg kg^{-1} and propofol 2–3 mg kg^{-1}. A laryngeal mask was inserted and the patient's lungs ventilated with 66% nitrous oxide in oxygen and isoflurane to an end-tidal concentration of 0.35–0.4% (MAC 1.0) and an end-tidal carbon dioxide concentration of 4.5–5.0% (Datex Capnomac). Patients were allocated randomly, using sealed envelopes, to receive two doses of either vecuronium 0.05 mg kg^{-1} or a similar volume of saline. The two groups were similar; there were seven females and 13 males with a mean age of 45.6 yr in the vecuronium group and 10 females and 16 males with a mean age of 46.8 yr in the saline group.

After a 10-min stabilization period, the AER was monitored for a period of 1024 sweeps before and after each dose of vecuronium or placebo and before and after stimulation by laryngoscopy for 20 s. Pa and Nb amplitudes and latencies were determined at

---

C. E. RICHMOND*, FRCA, A. MATSON†, FRCA, C. THORNTON, PHD, C. J. DORÉ, BSC, D. E. F. NEWTON, FRCA, Department of Anaesthesia, Northwick Park Hospital, Academic Department of Anaesthesia, St Mary's Hospital Medical School and Northwick Park Institute for Medical Research, Harrow, Middlesex HA1 3UJ. Accepted for publication: October 18, 1995.

Present addresses:

*Royal National Throat, Nose and Ear Hospital, Grays Inn Road, London.

†West Middlesex Hospital, Isleworth, London.

Correspondence to C.E.R. at Northwick Park Hospital.

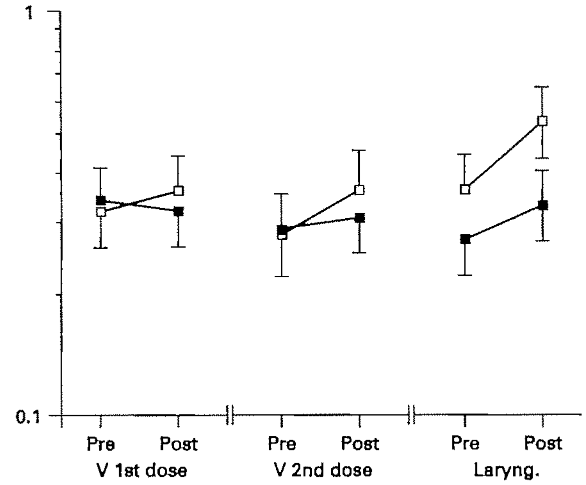


Figure 1 Mean (95 % confidence intervals) Pa amplitudes before and after each dose of vecuronium (V) (■) or saline (□), and before and after laryngoscopy (laryng.).

each time and analysis of variance was performed on $\log_{10}$ transformed data. The effect of drug or placebo was assessed between patients, and the effect of the time when it was given and the interaction between drug and time were assessed within patients. The probability level at which the null hypothesis was rejected was $P < 0.05$.

Overall, laryngoscopy caused a highly significant increase in Pa amplitude of 36 % ($P = 0.008$) and a reduction in Nb latency of 5.7 % ($P = 0.05$). This powerful stimulatory effect was not modified significantly by vecuronium compared with saline (fig. 1 shows the mean and 95 % confidence intervals (CI) for Pa amplitude). In the vecuronium group, mean Pa amplitude (µV) before laryngoscopy was 0.27 (95 % CI 0.22–0.34), increasing to 0.33 (0.27–0.4) after laryngoscopy. In the saline group, equivalent values were 0.36 (0.3–0.44) before and 0.53 (0.43–0.64) after laryngoscopy. Nb latency (mS) equivalent values in the vecuronium group were 62.2 (58.5–66.1) before and 59.0 (55.5–62.6) after laryngoscopy and in the saline group, 54.8 (51.6–58.2) before and 51.3 (48.3–54.5) after laryngoscopy.

In unstimulated patients, before laryngoscopy, there was no significant effect of vecuronium on any AER variable compared with the saline group. With respect to the first dose of vecuronium or saline, mean Pa amplitudes (µV) were: 0.34 (0.28–0.41) before vecuronium, 0.32 (0.26–0.39) after vecuronium, 0.32 (0.26–0.39) before saline, 0.36 (0.29–0.44) after saline. Equivalent values for Nb latency (mS) were: 57.5 (54.1–61.1) before vecuronium, 57.2 (53.9–60.8) after vecuronium, 56.4 (53.1–59.9) before saline, 57.5 (54.1–61.1) after saline. With respect to the second dose of vecuronium or saline, mean values for Pa amplitude were: 0.29 (0.23–0.35) before vecuronium, 0.31 (0.25–0.38) after vecuronium, 0.28 (0.23–0.35) before saline, 0.36 (0.3–0.45) after saline. Equivalent values for Nb latency (mS) were 62.1 (58.4–66.0) before vecuronium, 60.6 (57.0–64.3) after vecuronium, 56.8 (53.5–60.4) before saline, 57.4 (54.1–61.0) after saline.

The haemodynamic changes with laryngoscopy were also highly significant in both groups. Mean changes in heart rate was 6.6 (SEM 1.9) beat min^{-1} for the vecuronium group and 8.2 (1.9) beat min^{-1} for the saline group, from an average baseline of 58 beat min^{-1} ($P < 0.001$). Mean changes in systolic arterial pressure was 16.6 (SD 2.7) mm Hg in the vecuronium group and 18.5 (3.4) mm Hg in the saline group from an average baseline value of 95 mm Hg ($P < 0.001$). There was no statistically significant difference between the vecuronium and saline groups.

Comment

There was no clinically significant effect on the AER when vecuronium was given during steady state anaesthesia in unstimulated patients. Forbes, Cohen and Eger demonstrated a 25 % reduction in halothane requirements in humans after administration of pancuronium 0.1 mg kg^{-1} [1]. They suggested that pancuronium reduced MAC by abolishing muscle spindle afferent input to the reticular activating system, causing cortical depression. All neuromuscular blocking agents should reduce anaesthetic requirements to the same degree at equipotent doses. In this study, we should have seen a measurable change in the AER but we did not. Fahey and colleagues were also unable to find a change in the MAC of halothane in patients given pancuronium 0.1 mg kg^{-1}, vecuronium 0.1 mg kg^{-1} or atracurium 0.5 mg kg^{-1} [3]. Sessler, Olofsson and Chow, using frequency of spontaneous lower oesophageal contractions as a measure of anaesthetic depth, showed that the MAC of halothane in patients paralysed with vecuronium 0.1 mg kg^{-1} did not differ from that in unparalysed patients [4]. Schwartz, Navedo and Berman have shown that pancuronium 0.1 mg kg^{-1} administered to dogs given isoflurane, caused an increase in the percentage of the EEG that was isoelectric [2] compared with burst suppression; this was dose-related and reversible. They also suggested that reduced proprioceptive afferent activity caused the cortical depression.

In contrast with the effect of vecuronium, we have demonstrated that laryngoscopy produced lightening of depth of anaesthesia as measured by the AER. This effect was independent of the presence of neuromuscular block and coincided with the haemodynamic response to laryngoscopy.

References

1. Forbes AR, Cohen NH, Eger EI. pancuronium reduces halothane requirement in man. *Anesthesia and Analgesia* 1979; 58: 497–499.
2. Schwartz AE, Navedo AT, Berman MF. Pancuronium increases the duration of electroencephalogram burst suppression in dogs anaesthetized with isoflurane. *Anesthesiology* 1992; 77: 686–690.
3. Fahey MR, Sessler DI, Cannon JE, Brady K, Stoen R, Miller RD. Atracurium, vecuronium and pancuronium do not alter the minimum alveolar concentration of halothane in humans. *Anesthesiology* 1989; 71: 53–56.
4. Sessler DI, Olofsson CI, Chow F. Low esophageal contractility predicts movement during skin incisions; Vecuronium does not decrease the MAC of halothane *Anesthesia and Analgesia* 1988; 67: S201.

5. Thornton C. Evoked potentials in anaesthesia. *European Journal of Anaesthesiology* 1991; **8**: 89–107.
6. Jordan C, Weller C, Thornton C, Newton DEF. Monitoring evoked potentials during surgery to assess the level of anaesthesia. *Journal of Medical Engineering and Technology* 1995; **19**: 77–79.

British Journal of Anaesthesia 1996; 76: 449–451

Comparison of ondansetron and prochlorperazine for the prevention of nausea and vomiting after adenotonsillectomy†

A. A. VAN DEN BERG

Summary

This study has compared the incidences of nausea, vomiting and headache after ondansetron 0.06 mg kg^{-1} i.v., prochlorperazine 0.2 mg kg^{-1} i.m. and prochlorperazine 0.1 mg kg^{-1} i.v. given during induction of general anaesthesia to 282 patients undergoing adenotonsillectomy. The cardiovascular effects of the drugs were similar. After operation, nausea *per se* and vomiting *per se* occurred with similar frequency, in between 6% and 11% and 11% and 19%, respectively, in each test group. Nausea and vomiting in the same patient was reduced from 29% to 2% by i.v. ondansetron ($P < 0.0005$) and to 3% by i.m. prochlorperazine ($P < 0.0005$), and appeared to be less severe in these groups. Headache was most frequent after i.v. ondansetron (35%: $P < 0.05$), but occurred with similar frequency after i.m. prochlorperazine (32%) and i.v. prochlorperazine (29%). (*Br. J. Anaesth.* 1996; **76**: 449–451)

Key words

Pharmacology, ondansetron. Pharmacology, prochlorperazine. Vomiting, antiemetics. Vomiting, nausea. Surgery, otolaryngological.

Retching and vomiting after tonsillectomy are undesirable as they aggravate pain and may predispose to haemorrhage. The incidence of postoperative vomiting after adenotonsillectomy in this institution, where many patients undergoing tonsillectomy are adults, is about 30% [1]. Studies on the prophylactic use of antiemetics have revealed that prochlorperazine 0.2 mg kg^{-1} i.m. or 0.1 mg kg^{-1} i.v. is more effective than either metoclopramide 0.15 mg kg^{-1} orally or i.v., or droperidol 0.037 mg kg^{-1} i.v. [2]. While ondansetron 0.06 mg kg^{-1} i.v. has proved superior as a prophylactic antiemetic compared with metoclopramide [3] and droperidol [4], the relative efficacies of ondansetron and prochlorperazine have not been investigated.

This study has compared the efficacy of ondansetron 0.06 mg kg^{-1} i.v., prochlorperazine 0.2 mg kg^{-1} i.m. (as per licensing regulations in Europe) and prochlorperazine 0.1 mg kg^{-1} i.v. (as per licensing regulations in North America) [5]. Prochlorperazine given i.v. may cause hypotension or hypertension [5] and ondansetron may cause headache, and therefore this study also assessed the effects immediately after administration on heart rate and arterial pressure and, after operation, on headache.

Methods and results

The study was designed with respect to experience gained during studies of antiemetics in this hospital [2]. Here, non-Arabic-speaking British and Filipino nurses care for patients in the postoperative recovery and surgical wards. Language constraints, combined with the problem of eliciting subjective complaints from children, precluded queries regarding nausea in the recovery ward.

With Hospital Ethics Committee approval and parent (or guardian) consent, 282 ASA I–II Saudi nationals of all ages presenting for routine tonsillectomy (with or without adenoidectomy) were allocated randomly on arrival in the operating room to receive saline (as control) or one of the three antiemetic formulations with induction of anaesthesia.

Premedication comprised temazepam 0.5 mg kg^{-1} as elixir or capsules given orally, and EMLA cream applied to the dorsum of the left hand, 1.5 h before surgery. In theatre, routine monitoring devices (electrocardiogram, non-invasive automatic arterial pressure device, oxygen saturation monitor) were applied, an i.v. cannula inserted and preoxygenation commenced. Anaesthesia was induced with thiopentone 4.0 mg kg^{-1}, atracurium 0.6 mg kg^{-1} and nalbuphine 0.2 mg kg^{-1}, after which the appropriate test drug was administered (ondansetron 0.06 mg kg^{-1} i.v., prochlorperazine 0.2 mg kg^{-1} i.m., prochlorperazine 0.1 mg kg^{-1} i.v. or saline 1–2 ml). The larynx was sprayed with aerosolized lignocaine (10%) and a tracheal tube inserted. Heart rate and arterial pressures were recorded 1, 4, 7 and 10 min after tracheal intubation to assess the immediate cardiovascular effects of the test drugs.

Anaesthesia was maintained with 0.8% isoflurane and 67% nitrous oxide in oxygen. Respiration was controlled using an Ohmeda AV7700 ventilator with standardized respiratory variables and the Bain circuit to maintain an end-tidal carbon dioxide concentration of 4.5–5.0 kPa (Hewlett Packard 47210A Capnometer). Ringer's lactate or glucose–saline was infused during operation at a rate of 8 ml kg^{-1} h^{-1} and continued after operation at a rate of 2.0 ml kg^{-1} h^{-1} until oral fluids were tolerated. Dur-

---

ANTON A. VAN DEN BERG, MB, CHB, FRCA, Department of Anaesthesia, Riyadh Military Hospital, PO Box 7897, Riyadh 11159, Kingdom of Saudi Arabia. Accepted for publication: November 7, 1995.

†Presented in part at the 3rd European Society of Anaesthesiologists, Paris, April 29–May 3, 1995.

Table 1 Patient characteristics and postoperative morbidity data (mean (SD)). Incidence data are given as number of patients, incidence and percentage. DOA = Duration of anaesthesia. *$P < 0.05$, **$P < 0.025$, ***$P < 0.0005$ compared with saline (placebo)

	Saline			Prochlorperazine i.m.			Prochlorperazine i.v.			Ondansetron i.v.		
Patient numbers	69			72			71			70		
Sex (M:F)	43:26			44:28			43:28			43:27		
Age (yr)	18.1 (2–61)			19.4 (3–60)			18.4 (2–58)			17.8 (2–65)		
Weight (kg)	37.7 (22.4)			39.9 (26.1)			39.8 (27.6)			40.2 (26.7)		
DOA (min)	36.6 (20.4)			36.2 (20.2)			34.3 (15.2)			37.2 (21.3)		
Recovery ward												
Time (min)	30.5 (13.6)			29.2 (10.0)			28.1 (9.5)			29.8 (9.7)		
Nalbuphine	69	1	1%	72	3	4%	71	3	4%	70	4	6%
Prochlorperazine	69	1	1%	72	0	0%	71	0	0%	70	0	0%
Vomiting	69	1	1%	72	1	1%	71	1	1%	70	1	1%
Surgical ward												
Nalbuphine	69	2	3%	72	5	7%	71	2	3%	70	10	14%
Paracetamol	69	48	70%	72	49	68%	71	50	70%	70	49	70%
Prochlorperazine	60	4	6%	72	3	4%	71	4	6%	70	2	3%
Nausea	51	5	10%	61	8	11%	53	4	8%	53	3	6%
Vomiting	69	13	19%	72	13	18%	71	9	13%	70	8	11%
Nausea with vomiting	51	15	29%	61	2***	3%	53	11	21%	53	1***	2%
Absence of nausea or vomiting	69	37	54%	72	49	68%	71	47	66%	70	58	83%***
Severity of vomiting												
total vomiters		28			15			20			9	
single vomiters		10	36%		11**	73%		10	50%		7*	78%
multiple vomiters		18	64%		4**	27%		10	50%		2*	22%
Onset of PONV Mean (SD) (h)	5.68 (3.30)			7.65 (5.19)			6.25 (3.50)			5.72 (4.97)		
Headache	50	8	16%	63	20	32%	55	16	29%	55	19*	35%

ing surgery, after the initial 1,-, 4-, 7- and 10-min recordings of heart rate and arterial pressure, any increases in heart rate or increases in systolic arterial pressure $> 20\%$ of pre-induction values were treated with esmolol 2.0–3.0 mg kg^{-1} i.v. At the end of anaesthesia, residual neuromuscular block was antagonized with neostigmine 0.035 mg kg^{-1} and atropine 0.017 mg kg^{-1}. Nalbuphine 0.1 mg i.v. or 0.2 mg kg^{-1} i.m., paracetamol 10 mg kg^{-1} and prochlorperazine 0.2 mg kg^{-1} i.m. were prescribed to treat postoperative pain and sickness at the discretion of nursing staff.

The test drugs were coded and, to ensure blindness, all documentation was appropriately endorsed. Before induction of anaesthesia, note was made of patient details, antiemetic group, heart rate (HR), and systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressures. At termination of surgery and anaesthesia, duration of surgery was noted and any vomiting or retching immediately after extubation. Nurses in the recovery ward recorded details of vomiting, retching, extrapyramidal movements, antiemetic and analgesic requirements. During the first 24-h postoperative period, note was made by ward nurses of nausea, retching, vomiting or extrapyramidal reactions, and of antiemetic and analgesic drugs given. On the morning after surgery the author, also blinded to the test drug, visited the ward to review drug, temperature, fluid balance and nursing records. In addition, each patient or, in the case of younger children, their relative or guardian, was interviewed with respect to nausea, retching, vomiting and headache.

Data were analysed using analysis of variance, Student's t and chi-square tests with Yates' correction, where appropriate. To compare the effects on HR and arterial pressures, the areas under the time curves for HR, SAP, DAP and MAP were computed for each patient using the trapezoidal rule, and differences between drugs tested using two-way analysis of variance and the technique of Scheffé [6]. Chi-square tests were used to compare nausea, vomiting and postoperative drug requirements. The effects of the antiemetics in modifying the severity of vomiting were assessed by comparing the numbers of single and multiple vomiters in each group and the times when nausea, vomiting and retching occurred. Retching and vomiting were analysed collectively.

Of the 282 patients studied, 33 were aged 3 yr or less, 129 were aged 4–12 yr and 120 were older children or adults. One child refused premedication, but was included in the study and received i.v. ondansetron. The study groups were comparable in characteristics and need for analgesia and antiemetics in the recovery and surgical wards. No extrapyramidal reactions were reported and one patient in each group vomited in the recovery ward (table 1).

Analysis of HR and arterial pressures did not reveal any differences associated with the use of the test drugs.

In approximately 20 children in each group, communication difficulties prevented elucidation of nausea and headache in the postoperative ward. Where communication was possible, nausea *per se* occurred with similar frequency, in between 6% and 11% of patients, in each test drug group. Vomiting *per se*, without an accompanying complaint of nausea, also occurred with similar frequency, in between 11% and 19% of patients, in each test group. The incidences of the dual complaint of nausea and vomiting were also similar in those given placebo and i.v. prochlorperazine (29% and 21%, respectively), but greatly reduced (to 3% and 2%, respectively) in those given i.m. prochlorperazine and i.v. ondansetron ($P < 0.0005$, chi-square, both comparisons). The latter treatments also significantly modified the severity of vomiting by reducing the number of patients experiencing multiple vomits. However, the time to onset of nausea or vomiting was similar in all groups.

Those patients receiving saline (control) had the lowest incidences of postoperative headache (16 %), while those receiving i.m. prochlorperazine, i.v. prochloraperazine and i.v. ondansetron had higher, but similar, incidences (32 %, 29 % and 35 %, respectively). However, only the ondansetron–placebo difference was significant ($P < 0.05$).

Comment

This double-blind, controlled study was conducted to compare: the antiemetic efficacies of ondansetron 0.06 mg kg^{-1} i.v., prochlorperazine 0.2 mg kg^{-1} i.m. and prochlorperazine 0.1 mg kg^{-1} i.v., given during induction of anaesthesia for in-patient adenotonsillectomy; the immediate effects of these drugs on HR and arterial pressure; and the effects on the incidence of headache in the postoperative period.

Neither prochlorperazine nor ondansetron reduced the incidence of postoperative nausea *per se* or vomiting *pe se*. I.m. prochlorperazine and i.v. ondansetron markedly reduced the number of patients experiencing nausea associated with vomiting, and also reduced the severity of vomiting in those who did vomit. Absence of PONV occurred most frequently in those given i.v. ondansetron.

The test drugs produced no adverse cardiovascular effects within 10 min of administration, but ondansetron was associated with the highest incidence of postoperative headache.

A problem in paediatric anaesthesia is the propensity of children to develop extrapyramidal reactions if given an antiemetic drug (such as metoclopramide, a phenothiazine or droperidol) which has an anti-dopaminergic mode of action. Allied to the risk of inducing changes in arterial pressure that may follow i.v. injection of a phenothiazine [5], this rationalized the testing of the smaller dose of i.v. prochlorperazine (0.1 mg kg^{-1}, equal to 50 % of the recommended i.m. dose [5]). While no adverse cardiovascular or extrapyramidal events occurred after either prochlorperazine treatments, the smaller dose of prochlorperazine given i.v. was conspicuous in not alleviating sickness.

Ondansetron exerts its effect via inhibition of 5-hydroxytryptamine, but may thereby cause headache. Although headache occurred most commonly in those given ondansetron (35 %), surprisingly similar incidences were reported in those given i.m. prochlorperazine (32 %) and i.v. prochlorperazine (29 %). Headache is, however, a less debilitating and hazardous morbidity after adenotonsillectomy than nausea and vomiting and should not inhibit the use of ondansetron in these patients.

Acknowledgements

I am indebted to Drs S. Bandey, M. Rabiah and H. Al Nasser (ear, nose and throat surgeons); Drs E. Halliday, R. Dunning and D. Savva (anaesthetists); Mr R. Ashford (medical photographer); Mrs J. White, Mrs Irene Beirne and Ms Patricia Boylan (anaesthesia personal assistants) and Glaxo Laboratories for their combined contributions to this study.

References

1. van den Berg AA, Honjol NM, Rama Prabhu NV, Datta S, Rozario CJ, Muraleedaran R, Savva D. Analgesics and ENT surgery. A clinical comparison of the intraoperative, recovery and postoperative effects of buprenorphine, diclofenoc, fentanyl, morphine, nalbuphine, pethidine and placebo given intravenously with induction of anaesthesia. *British Journal of Clinical Pharmacology* 1994; **38**: 533–544.
2. van den Berg AA. Prochlorperazine and vomiting after eye surgery. *Anaesthesia* 1987; **42**: 897.
3. Raphael JH, Norton AC. Antiemetic efficacy of ondansetron in laparoscopic surgery: randomized, double blind comparison with metoclopramide. *British Journal of Anaesthesia* 1993; **71**: 845–848.
4. Alon E, Himmelseher S. Ondansetron in the treatment of postoperative vomiting: a randomized double-blind comparison with droperidol and metoclopramide. *Anesthesia and Analgesia* 1992; **75**: 561–565.
5. Reynolds JEF. Anxiolytics, sedatives, hypnotics and neuroleptics. In: Reynolds JEF, ed. *Martindale. The Extra Pharmacopoeia*, 29th Edn. London: The Pharmaceutical Press, 1989; 706–776.
6. Scheffe H. A method of judging all controls using the analysis of variance. *Biometrika* 1953; **40**: 87–104.

British Journal of Anaesthesia 1996; **76**: 452–455

Smaller children have greater bupivacaine plasma concentrations after ilioinguinal block

T. SMITH, P. MORATIN AND H. WULF

Summary

We have measured plasma concentrations of bupivacaine after ilioinguinal block in children of different sizes. We studied 14 children with weights 10–15 kg and 17 children with weights 15–30 kg. Each child received 0.5% bupivacaine 0.25 ml kg^{-1} (1.25 mg kg^{-1}) (Carbostesin, Astra, Germany). Venous blood was obtained before the block (control) and at 5, 10, 15, 20, 30 and 60 min after block. Mean maximal concentration in the 10–15-kg group (1.5 (SD 0.9)mg litre^{-1}, range 0.43–4.0 mg litre^{-1}, at 18 (5) min) was significantly higher ($P < 0.05$) than that in the 15–30-kg group (0.9 (0.3)mg litre^{-1} range 0.35–1.34 mg litre^{-1}, at 16 (5) min). In the 10–15-kg group, unexpectedly high (up to 4 mg litre^{-1}) bupivacaine concentrations were observed and often concentrations remained high (> 2 mg litre^{-1}) at 60 min. We conclude that smaller children appear to differ in the pharmacokinetic handling of bupivacaine. The maximum safe plasma concentration of bupivacaine in small children, although not clearly established, is likely to be approximately 4 mg litre^{-1}. We recommend, therefore, that a dose of bupivacaine 1.25 mg kg^{-1} should not be exceeded in the perioperative period when performing ilioinguinal block in children < 15 kg in weight. (*Br. J. Anaesth.* 1996; **76**: 452–455)

Key words

Anaesthetic techniques, regional, inguinal. Anaesthetics local, bupivacaine. Pharmacokinetics, bupivacaine. Anaesthesia, paediatric. Children.

Ilioinguinal block with bupivacaine is used widely in children undergoing inguinal hernia or orchidopexy surgery. Some blocks are ineffective and often children require bilateral surgery; in these children repeated or bilateral blocks may be indicated. The question of how safely additional ilioinguinal blocks can be performed in small children requires knowledge of bupivacaine plasma concentrations after a single block. Stow and colleagues [1] and Epstein and colleagues [2] reported reassuringly low concentrations in children. However, their studies were small and failed to consider the possible differences related to child size. In this study, we have compared plasma concentrations of bupivacaine after ilioinguinal block in two groups of children: 10–15 kg and 15–30 kg in weight.

Methods and results

After obtaining Ethics Committee approval and written informed consent from the parents, we studied 14 children weighing 10–15 kg and 17 children weighing 15–30 kg. All children were ASA I and not receiving any medications before hospital admission. All were undergoing elective surgery for inguinal hernia, hydrocele or orchidopexy.

Premedication comprised EMLA cream over a prominent vein and midazolam 0.3 mg kg^{-1} rectally. An upper limb vein was cannulated, atropine 0.01 mg kg^{-1} given and anaesthesia induced with methohexitone 1–2 mg kg^{-1}. Neuromuscular block for intubation was produced with suxamethonium 1.5 mg kg^{-1}. After intubation, anaesthesia was maintained with 0.5–2 % isoflurane and 50–70 % nitrous oxide in oxygen. Another vein was cannulated in the opposite upper limb to the first for blood sampling. An ilioinguinal block with 0.5 % bupivacaine 0.25 ml kg^{-1} (Carbostesin, Astra, Germany) was then performed. Using a 0.55-mm diameter Sprotte needle (Pajunk, Germany), 80 % of bupivacaine was injected (after negative aspiration for blood) two finger breadths of the child medial to the anterior superior iliac spine at the depth where loss of resistance occurred as the needle pierced the external oblique fascia (here the ilioinguinal and iliohypogastric nerves run between the external oblique and internal oblique muscles). The remaining 20 % was injected s.c. in lines radiating inferiorly and medially from the injection point (to block cutaneous nerve fibres missed by ilioinguinal nerve block).

The child then underwent surgery and blood samples were obtained at 5, 10, 15, 20, 30, 45 and 60 min after the block. K-EDTA tubes were used and blood was centrifuged, plasma extracted and frozen at −20 °C until analysis.

Plasma concentrations of bupivacaine were measured by high pressure liquid phase chromatography, as described previously [3].

T. SMITH*, MB, BS, DA, P. MORATIN†, MD, H. WULF, MD, PHD, Department of Anaesthesiology and Intensive Care Medicine, University Hospital, Schwanenweg, 24105 Kiel, Germay. Accepted for publication: October 16, 1995.

*Present address for correspondence: Department of Anaesthesia, Taunton and Somerset Hospital, Musgrove Park, Taunton TA1 5DA, Somerset.

†Present address: Department of Anaesthesiology and Intensive Care Medicine, Klinikum, Albert Schweizer Strasse 10, 95326 Kulmbach, Germany.

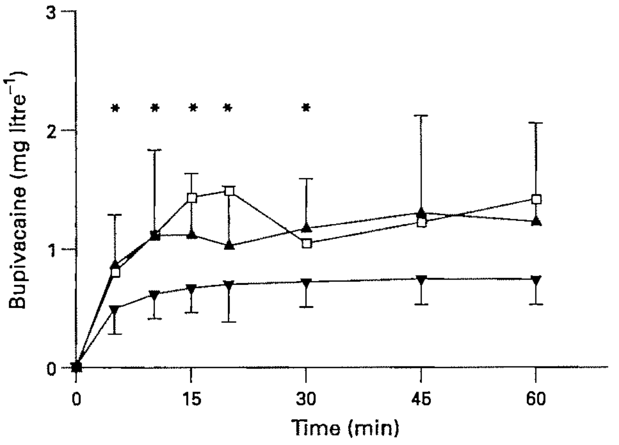


Figure 1 Bupivacaine plasma concentrations after ilioinguinal block with 0.5 % bupivacaine 0.25 ml kg^{-1} (1.25 mg kg^{-1}) in the 10–15 kg ($n = 14$) (▲) and 15–30 kg ($n = 17$) (▼) groups. □ = Values of an individual 12-kg child, showing a second increase in plasma bupivacaine concentration coinciding with emergence from anaesthesia (extubation at 47 min). *$P < 0.05$ between the two groups.

With GraphPad Prism 1.03 software and an IBM compatible PC, ANOVA, linear regression analysis and the Mann–Whitney *U* test were used to evaluate the data. $P < 0.05$ was considered significant. Data are expressed as mean (SD).

In the 10–15-kg group, mean maximum plasma bupivacaine concentration was 1.5 (SD 0.9) mg litre^{-1} (range 0.43–4.0 mg litre^{-1}) at a mean time of 18 (5) min after the block (fig. 1). The corresponding values for the 15–30-kg group were 0.9 (0.3) (0.35–1.34) mg litre^{-1} at 16 (5) min. The difference in maximum plasma concentration observed between the two weight groups was significant ($P < 0.05$), as were the differences at 5, 10, 15, and 30 min ($P < 0.05$). Four of the 10–15-kg children had maximum concentrations exceeding 2 mg litre^{-1} whereas none of the larger children exceeded this value.

There were no complications and, in particular, no side effects attributable to systemic toxicity of bupivacaine.

Comment

Our bupivacaine dose of 1.25 mg kg^{-1} was considerably less than the maximum recommended dose for peripheral nerve blocks in children of 2 mg kg^{-1} [4, 5]. Despite this, the 10–15-kg group had unexpectedly high plasma bupivacaine concentrations, the highest bordering on the generally accepted toxic range for adults of > 4 mg litre^{-1} [6, 7]. In contrast, concentrations in the 15–30-kg group were low, consistent with the results of previous studies by Stow and colleagues [1] and Epstein and colleagues [2]. Stow and colleagues, using 1.25 mg kg^{-1}, reported a mean peak concentration of 0.79 mg litre^{-1} at 22.3 min in children with a mean weight of 20 kg; the highest individual concentration observed was not reported. Epstein and colleagues, using 2 mg kg^{-1}, reported a mean concentration of 1.35 mg litre^{-1} at 26 min in 14 children with a mean weight of 18.6 kg; the highest observed concentration was 2.23 mg litre^{-1}.

Our study, and those of Stow and Epstein, showed that plasma concentrations may be near their maximum even 1 h after the block. This is different from the rapid decrease in bupivacaine plasma concentrations observed in adult studies [8–11]. Interestingly, in some cases we observed a second peak of plasma bupivacaine concentration coinciding with the end of anaesthesia (see fig. 1); this was probably the result of increased local anaesthetic absorption resulting from the hyperdynamic circulation associated with emergence from anaesthesia and awake extubation.

There are three important questions arising from this study. First, what are the possible causes for the observed differences between the two sizes of children? There are three possibilities: (i) more rapid absorption because of increased cardiac output in relation to body mass; (ii) decreased tissue uptake—Mather, Long and Thomas [12] observed that during the first 30 min, tissue uptake is much more important than metabolism in determining bupivacaine venous concentration; (iii) decreased drug metabolism—bupivacaine, in common with other amide local anaesthetics, is metabolized almost completely in the liver before excretion [13]. Infants have reduced microsomal enzyme metabolism [14, 15] and elimination half-life is prolonged. These differences are greatest in neonates, and therefore the likelihood of high bupivacaine plasma concentrations after ilioinguinal block is probably even higher in this group than in our 10–15-kg group.

It is possible that administration of methohexitone could have decreased bupivacaine metabolism in the smaller children. Both drugs are metabolized in the liver but detailed knowledge of their metabolism is lacking [13, 16–18] and there are no data on possible interactions.

We believe that the probability of error in dose causing high plasma bupivacaine concentrations in our 10–15-kg group is very small, as all doses were checked by an observer. The wide range of maximum concentrations in the 15–30-kg group is consistent with other studies of plasma concentration of bupivacaine after local block [1, 2, 9–11]. The range in the 10–15-kg group was even greater; this could reflect differences in maturation of the children in terms of bupivacaine pharmacokinetics, and also the variable haemodynamics in such small children could be important.

Second, what concentration of plasma bupivacaine is safe in small children? The generally accepted toxic range for adults is an arterial plasma concentration exceeding 4 mg litre^{-1}. This implies that the acceptable venous plasma concentration is less than 4 mg litre^{-1}, as arterial bupivacaine concentrations are consistently higher than corresponding venous concentrations [9]. The value of 4 mg litre^{-1} was proposed by Jordfeldt and colleagues [6] in 1968 and was based on toxicity studies in dogs. Subsequently, Moore, Balfour and Fitzgibbons [7] reported a case history in which an arterial bupivacaine plasma concentration of 5.1 mg litre^{-1} caused convulsions which ceased when the concentration approached 3.5 mg litre^{-1}.

However, Denson and colleagues [19] have shown that patients may be asymptomatic with venous plasma bupivacaine concentrations exceeding 6 mg $litre^{-1}$, but symptomatic with concentrations as low as 2.1 mg $litre^{-1}$. In the study of Denson and colleagues, differences may have been caused by variations in bupivacaine-binding plasma proteins. Normally, approximately 92 % of plasma bupivacaine is protein bound, mainly to α_1 acid glycoprotein and albumin [20]. It is free bupivacaine that causes toxicity, a venous concentration of 0.24 mg $litre^{-1}$ probably represents the threshold in adults [19]. Competition for plasma protein binding sites by other drugs may increase the free plasma bupivacaine concentration and thus risk of toxicity. Atropine [21] and diazepam [22] (and therefore probably other benzodiazepine drugs) have no effect on bupivacaine plasma protein binding. However, diphenylhydantoin, quinidine, pethidine, and desipramine have all been shown to increase the free fraction of plasma bupivacaine [21].

The rate of increase in local anaesthetic plasma concentration may be more important than the actual concentration [23]. Sedative medications (and general anaesthetics) may increase considerably the threshold for CNS toxicity for local anaesthetic agents [6].

Children and adults may differ in sensitivity to bupivacaine. In animal studies, immature pigs [24] and sheep [25] have been found to be more resistant to bupivacaine toxicity, but young mice are more prone to CNS toxicity than adult mice [26]. The only data related to human children originate from the case reports of McClosky, Huan and Deshpande [28] of systemic toxicity after continuous caudal bupivacaine infusions. A 3.9-kg neonate experienced cardiovascular toxicity with a plasma bupivacaine concentration of 5.6 mg $litre^{-1}$. An 8-yr-old, 45-kg child developed fits with a concentration of 6.6 mg $litre^{-1}$. These reports suggest that it is wise not to exceed a venous concentration of 4 mg $litre^{-1}$ in children. Our findings suggest that while bilateral or repeat blocks are probably safe in children exceeding 15 kg, they could lead to plasma bupivacaine concentrations in the toxic range in smaller children. Neonates have been shown to have reduced protein binding of bupivacaine with the free fraction accordingly increased [28], and therefore the risk of toxicity may be even higher in this group.

There are no reports of toxic adverse reactions after ilioinguinal block in children. However, it must be remembered that the block is almost always performed during general anaesthesia.

Third, could the ilioinguinal block technique be altered to give lower plasma bupivacaine concentrations? There are two possible changes to our ilioinguinal block technique which may result in lower plasma bupivacaine concentrations. The first is the use of adrenaline to reduce the rate of absorption. Hayse-Gregson, Achola and Smith [29] studied the changes in haemodynamics and plasma catecholamine concentrations in adults after field block for inguinal herniorrhaphy using lignocaine and adrenaline 1 in 200000. They found a significant increase in heart rate and potentiation of arrhythmias. The other major possibility is the use of 0.25 % bupivacaine instead of 0.5 %. It is our experience that 0.25 % bupivacaine gives a less rapid and less reliable block, but a controlled trial is needed to assess this. Finally, we are aware that most anaesthetists do not use our technique of injecting 20 % of bupivacaine inferiorly and medially s.c. We have found this modification provides very reliable analgesia for skin incision. All children received the same block technique so this modification could not have caused the differences observed between the two groups.

We suggest that, although the toxic venous plasma bupivacaine concentration in small children has not been defined, it would seem unwise to exceed 4 mg $litre^{-1}$. We conclude that very small children differ from larger ones in their pharmacokinetic handling of bupivacaine and are likely to have higher plasma concentrations when bupivacaine is administered according to body weight. We recommend that a total dose of bupivacaine 1.25 mg kg^{-1} should not be exceeded in the perioperative period when performing ilioinguinal blocks in children less than 15 kg in weight.

Acknowledgements

We acknowledge the expert assistance and hard work of laboratory technician Frau Margret Betz, and of our colleagues Dr Gunda Comberg, Dr Marc Petersen and Dr Stefanie Brümmer-Smith of the Department of Anaesthesiology and Intensive Care Medicine, University of Kiel.

References

1. Stow PJ, Scott A, Phillips A, White JB. Plasma bupivacaine concentrations during caudal analgesia and ilioinguinal–iliohypogastric nerve block in children. *Anaesthesia* 1988; **43**: 650–653.
2. Epstein RH, Larijani GE, Wolfson PJ, Ala-Kokko TI, Boerner TF. Plasma bupivacaine concentrations following ilioinguinal–iliohypogastric nerve blockade in children. *Anesthesiology* 1988; **69**: 1988.
3. Wulf H. Gleim M, Schele HA. Plasma concentrations of bupivacaine after lumbar sympathetic block. *Anesthesia and Analgesia* 1994; 79: 918–920.
4. Atkinson RS, Rushman GB, Davies NJH. Regional anaesthesia. In: *Lee's Synopsis of Anaesthesia*, 11th Edn. London: Butterworth–Heinemann, 1993; 613–690.
5. Brown TCK, Schulte-Steinberg O. Neural blockade for pediatric surgery. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*, 2nd Edn. Philadelphia: Lippincott, 1988; 669–692.
6. Jorfeldt L, Lofstrom B, Pernow B, Persson B, Wahren J, Widmen, B. The effect of local anaesthetics on the central circulation and respiration in man and dog. *Acta Anaesthesiologica Scandinavica* 1968; **12**: 153–169.
7. Moore DC, Balfour RI, Fitzgibbons D. Conclusive arterial plasma levels of bupivacaine and the response to diazepam therapy. *Anesthesiology* 1979; **50**: 454–456.
8. Neill RS, Watson R. Plasma bupivacaine concentrations during combined regional and general anaesthesia for resection and reconstruction of head and neck carcinomata. *British Journal of Anaesthesia* 1984; **56**: 485–493.
9. Moore DC, Mather LE, Bridenbaugh LD, Balfour RI, Lysons DF, Horton WG. Arterial and venous plasma levels of bupivacaine following peripheral nerve blocks. *Anesthesia and Analgesia* 1976; **55**: 763–768.
10. Belfrage A, Berlin A, Lindstedt M, Raabe N. Plasma bupivacaine following pudendal block in labour. *British Journal of Anaesthesia* 1973; **45**: 1067–1069.

11. Wulf H, Gleim M, Maier C, Schulzeck S. Plasma concentrations of bupivacaine in celiac plexus block. *Regional Anaesthesia* 1995; **20** (3): 222–226.
12. Mather LE, Long J, Thomas J. The intravenous toxicity and clearance of bupivacaine in man. *Clinical Pharmacology and Therapeutics* 1971; **12**: 935.
13. Boyes RN. A review of the metabolism of amide local anaesthetic agents. *British Journal of Anaesthesia* 1975; **47**: 225–230.
14. Morgan DJ, McQuillan D, Thomas J. Pharmacokinetics and metabolism of the anilide local anaesthetics in neonates II: Etidocaine. *European Journal of Clinical Pharmacology* 1978; **13**: 359–365.
15. Mango R, Berlin A, Karlson K, Kjellmer I. Anaesthesia for caesarean section IV: Placental transfer and neonatal elimination of bupivacaine following epidural analgesia for elective Caesarean section. *Acta Anaesthesiologica Scandinavica* 1976; **20**: 141–147.
16. Tucker GT, Mather LE. Properties, absorption and disposition of local anesthetic agents. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*, 2nd Edn. Philadelphia: Lippincott, 1988; 47–110.
17. Breimer DD. Pharmacokinetics of methohexitone following intravenous infusion in humans. *British Journal of Anaesthesia* 1976; **48**: 643–649.
18. Hudson RJ, Stanski DR, Burch PG. Pharmacokinetics of methohexital and thiopental in surgical patients. *Anesthesiology* 1983; **59**: 215–219.
19. Denson DD, Myers JA, Hartrick CT, Pither CP, Coyle DE, Raj PP. The relationship between free bupivacaine concentration and central nervous system toxicity. *Anesthesiology* 1984; **61**: A211.
20. Tucker GT, Boyes RN, Bridenbaugh PO, Moore DC. Binding of anilide-type local anesthetics in human plasma. I: Relationships between binding, physiochemical properties and anesthetic activity. *Anesthesiology* 1970; **33**: 287–303.
21. Ghonheim MM, Pandya H. Plasma bupivacaine and its interaction with other drugs in man. *British Journal of Anaesthesia* 1974; **46**: 435–438.
22. Denson DD, Myers JA, Thompson GA, Coyle DE. The influence of diazepam on the serum protein binding of bupivacaine at normal and acidic pH. *Anesthesia and Analgesia* 1984; **63**: 980–984.
23. Scott DB. Evaluation of the toxicity of local anaesthetic agents in man. *British Journal of Anaesthesia* 1975; **47**: 56–61.
24. Badgwell JM, Heavner JE, Kytta JK. Bupivacaine toxicity in young pigs is age-dependent and is affected by volatile anesthetics. *Anesthesiology* 1990; **73**: 297–303.
25. Morishma HO, Pedersen H, Finster M, Sakuma K, Bruce SL, Gutsche BB, Stark RI, Covino BG. Toxicity of lidocaine in adult, newborn and fetal sheep. *Anesthesiology* 1981; **55**: 57–61.
26. Liu PL, Covino BM, Feldman HS. Effect of age on local anesthetic central nervous system toxicity in mice. *Regional Anesthesia* 1983; **10**: 57–60.
27. McClosky JJ, Huan SE, Deshpande JK. Bupivacaine toxicity secondary to continuous caudal epidural infusion in children. *Anesthesia and Analgesia* 1992; **75**: 287–290.
28. Mazoit JX, Denson DD, Samii K. Pharmacokinetics of bupivacaine following caudal anesthesia in infants. *Anesthesiology* 1988; **68**: 387–391.
29. Hayse-Gregson PB, Achola KJ, Smith G. Changes in haemodynamics and plasma catecholamine concentrations after field block for inguinal herniorraphy using lignocaine with adrenaline. *Anaesthesia* 1990; **45**: 7–10.

British Journal of Anaesthesia 1996; **76**: 456–458

Laryngeal mask airway performance: effect of cuff deflation during anaesthesia

G. N. MORRIS AND R. MARJOT

Summary

We studied the effect of deflating the laryngeal mask airway (LMA) cuff *in situ* on recorded respiratory tidal ventilation in 30 spontaneously breathing anaesthetized patients. Another 26 patients were studied in whom the LMA cuff was undisturbed. Deflation of the cuff to a pressure of 22 mm Hg (below an estimated arteriolar perfusion pressure of the pharyngeal mucosa), by removing approximately 50% of the recommended cuff injection volume, had a minimal effect on tidal ventilation ($P = 0.9$). This manoeuvre may have a role in minimizing transmitted cuff pressure on the adjacent pharyngeal mucosa. Complete cuff deflation, however, resulted in a 17% decrease in mean tidal ventilation ($P < 0.05$), with two patients (6%) demonstrating a substantial leak around the cuff and airway obstruction. The practice of complete cuff deflation during the recovery period from anaesthesia cannot be recommended. (*Br. J. Anaesth.* 1996; **76**: 456–458)

Key words

Complications, mucosal pressure. Equipment, masks anaesthesia.

The two principal functions of the cuff of the laryngeal mask airway (LMA) are to orientate the mask on inflation and to subsequently generate a low pressure seal around the laryngeal inlet. However, it has been shown to exert substantial pressures on the adjacent pharyngeal mucosa. This occurs even before full inflation with the manufacturer's recommended injection volumes and despite apparent accommodation by the pharynx [1].

The morbidity resulting from such pressures exceeding mucosal capillary perfusion pressure remains undetermined. Intra-cuff pressure monitoring is currently recommended by the manufacturer to avoid postoperative throat discomfort [2]. Several methods of limiting intra-cuff pressure have been suggested, including submaximal cuff inflation or partial deflation of the cuff during anaesthesia. These manoeuvres have recently been endorsed by the inventor of the device, Dr A. I. J. Brain [3].

This study was undertaken to determine the effect of LMA cuff deflation during anaesthesia on LMA performance.

Methods and results

After obtaining Hospital Ethics Committee approval and informed consent, we studied 56 adult ASA I or II unpremedicated patients (29 males) presenting for elective minor surgery. Anaesthesia incorporating spontaneous ventilation via an LMA was appropriate and not contraindicated for any patient.

An appropriately sized LMA (3 for females, 4 for males) was checked [2] and the pilot tube connected via a three-way tap to a 50-ml Plastipak syringe and a Spectramed pressure transducer (PIOEZ) with a recorder. The same transducer was calibrated against a mercury column and the zero point determined before each study (non-linear error < 2%). Each LMA cuff was evacuated to a pressure of −20 mm Hg. The syringe volume was then adjusted to the manufacturer's recommended injection volume (20 ml for size 3, 30 ml for size 4 LMA). This sealed system was not disrupted until the end of each study.

All patients were fasted and unpremedicated. Anaesthesia was induced with propofol 2–3 mg kg^{-1} and fentanyl 1 μg kg^{-1}. The LMA was inserted as described by the manufacturer [2] by one of the two investigators and the cuff inflated fully with the preset volume. Adequacy of placement was judged by the absence of any clinical or audible evidence of upper airway obstruction, examination of the capnography trace and the ease of positive pressure ventilation applied while the patients were apnoeic. The head and neck were then placed in a neutral position resting on one pillow. Anaesthesia was maintained with 1–2.5% isoflurane, and 60% nitrous oxide in oxygen; patients breathed spontaneously from a circle system. Each tidal volume was recorded during the study period using a Narkomed 4 (North American Drager) Spiromed positive displacement rotating lobe impeller (error < ±10 ml).

The patients were allocated to one of two groups (30 patients in group 1, 26 patients in group 2) and were studied 15 min after induction of anaesthesia. During this period, tidal volume recordings were

---

G. N. MORRIS*, MB, BS, MRCGP, FRCA, R. MARJOT, MB, BS, FRCA, Anaesthetic Department, Royal United Hospital, Combe Park, Bath BA1 3NG, Avon. Accepted for publication: October 17, 1996.

*Present address: Department of Anaesthesiology, University of Virginia, PO Box 238, Charlottesville, Virginia 22908, USA.

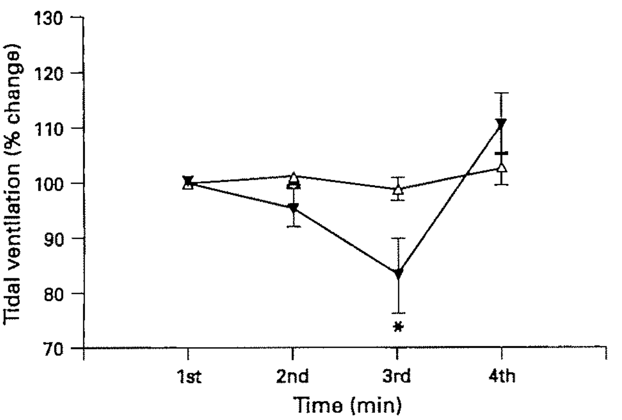


Figure 1 Mean (SEM) tidal ventilation plotted as a percentage of baseline recordings made during the first minute (1st). For group 1 (▼), recordings were made during the second (2nd), third (3rd) and fourth (4th) consecutive minutes with the LMA cuff deflated to 22 mm Hg intra-cuff pressure (2nd), fully deflated (3rd) and fully re-inflated (4th). For group 2 (△), all recordings were made with the LMA cuff unaltered over the same time period (2nd, 3rd, 4th). $*P = 0.05$ compared with baseline recordings in group 1.

made over 4 consecutive minutes. In group 1, for the first minute the LMA was undisturbed, for the second minute the cuff was deflated to a pressure of 22 mm Hg, for the third minute the cuff was fully deflated to −20 mm Hg, and for the fourth minute the cuff was re-inflated fully with the gas stored in the closed syringe system. Tidal volumes were recorded with the fresh gas flow turned off and the expiratory valve closed to make a closed circle system. Inspired and expired isoflurane and nitrous oxide concentrations remained constant throughout the readings. In group 2, patients were treated identically but tidal volumes were recorded over four consecutive 1-min periods without the cuff being altered in any way.

Within-group data were analysed using two-way analysis of variance (ANOVA) for repeated measures (Micosoft Excel). A probability value of less than 0.05 was considered to be significant. Data are presented as mean (SEM).

There was no difference between the groups in terms of age (group 1, 37 (range 21–80) yr; group 2, 37 (19–75) yr), sex ratio (group 1, 18 males, 12 females; group 2, 11 males, 15 females) or body mass index (group 1, 27.5 (0.6) kg m^{-2}; group 2, 25.4 (0.4) kg m^{-2}).

Intra-cuff pressures after initial inflation were substantial and increased during anaesthesia as cuff volume increased with diffusion of nitrous oxide into the cuff. Reduction in intra-cuff pressure to 22 mm Hg required removal of approximately 50 % of the initial cuff volume (size 4 LMA 16.3 (1) ml; size 3 LMA 10.7 (0.6) ml).

The mean respiratory tidal volume recorded during the first minute of the study period, before cuff deflation, was taken as baseline and plotted as 100 %. Subsequently recorded mean tidal volumes were plotted as a percentage of these values (fig. 1). Mean tidal volume in patients in group 1 decreased to 95 % of the baseline value when the cuff was deflated to 22 mm Hg ($P = 0.9$). The response to this degree of deflation was variable, and in eight patients (26 %) tidal ventilation increased slightly.

When the cuff was deflated fully, mean tidal volume decreased significantly to 83 % of baseline ($P = 0.035$). At this time, two patients (6 %) had no recordable tidal ventilation with noisy and partially obstructed breathing. When the cuff was re-inflated fully, mean tidal ventilation increased to 110 % of the original baseline value, and any obstruction was relieved. This increase was not significant compared with the baseline mean tidal ventilation ($P = 0.18$).

There was no significant change in the recorded mean tidal volumes of patients in group 2 throughout the study period (fig. 1).

Comment

Inflating the LMA cuff to the volume recommended by the manufacturer [2] results in transmitted pressures on the pharynx in excess of mucosal capillary perfusion pressure [1]. The morbidity resulting from these high transmitted pressures on the pharyngeal mucosa is unknown. There have been isolated reports of trauma to the posterior pharyngeal wall, uvula and large tonsils, and compression of the hypoglossal nerve [4], lingual artery [5] and recurrent laryngeal nerve [6]. Intra-cuff pressure monitoring is recommended but no acceptable level is stipulated [2]. Several methods of limiting intra-cuff pressure have been suggested, including submaximal cuff inflation or partial cuff deflation during anaesthesia [3].

We have studied, in spontaneously breathing anaesthetized patients, the effect of deflating the LMA cuff *in situ* on recorded respiratory tidal volumes. Mean respiratory tidal ventilation decreased as LMA cuff volumes (and pressures) were reduced. This effect was minimal when the cuff was deflated to a pressure of 22 mm Hg with the withdrawal of approximately 50 % of the initial inflation volume. Complete cuff deflation resulted in a significant decrease in recorded tidal ventilation. This may have resulted from tidal ventilation escaping around the sides of the partially and fully deflated LMA cuff or a degree of upper airway obstruction, or both. Two patients (6 %) demonstrated a substantial leak around the LMA cuff with clinical evidence of upper airway obstruction. The practice of some anaesthetists and recovery nursing staff to fully deflate the LMA cuff during the period of recovery from anaesthesia cannot be supported. This practice is contrary to the manufacturer's instructions [2] which states that deflation should only be performed when "the patient can open their mouth on command". There was a return to baseline mean tidal ventilation when the cuff was re-inflated fully (with the same gas), to the original cuff volume.

There was no change in the tidal volumes recorded in group 2 throughout the study, which would exclude any chance alteration in the level of surgical stimulus or depth of anaesthesia as being responsible for the changes observed in group 1.

We have demonstrated that the cuff of the LMA may be deflated to a pressure of 22 mm Hg (i.e. below the arteriolar perfusion pressure of the pharyngeal mucosa) with minimal effect on the recorded tidal ventilation, in spontaneously ventilating patients. The effect of this manoeuvre should, however, be assessed for each individual patient. Full deflation of the cuff results in a significant decrease in recorded tidal ventilation. The practice of complete cuff deflation during recovery from anaesthesia cannot be recommended.

References

1. Marjot R. Pressure exerted by the laryngeal mask airway cuff upon the pharyngeal mucosa. *British Journal of Anaesthesia* 1993; **70**: 25–29.
2. Brain AIJ. *The Intavent Laryngeal Mask; Instruction Manual*, 2nd Edn. Windsor: Colgate Medical Limited, 1991.
3. Brain AIJ. Course of the hypoglossal nerve in relation to the laryngeal mask airway. *Anaesthesia* 1995; **50**: 82–83.
4. Nagai K, Sakuramoto C, Goto F. Unilateral hypoglossal nerve paralysis after the use of the laryngeal mask airway. *Anaesthesia* 1994; **49**: 603–604.
5. Wyne JM, Jones KL. Tongue cyanosis after laryngeal mask airway insertion. *Anesthesiology* 1994; **80**: 1403.
6. Inomata S, Nishikawa T, Suga A, Yamashita S. Transient bilateral vocal cord paralysis after insertion of a laryngeal mask airway. *Anesthesiology* 1995; **82**: 787–788.

British Journal of Anaesthesia 1996; **76**: 459–460

Delayed forced air warming prevents hypothermia during abdominal aortic surgery

J. Karayan, D. Thomas, L. Lacoste, K. Dhoste, J. B. Ricco and J. Fusciardi

Summary

We have evaluated the efficacy of the delayed forced air warming during abdominal aortic surgery in 18 patients. Patients were allocated randomly to one of two groups: the control group ($n = 9$) received no intraoperative warming device; the Bair-Hugger group ($n = 9$) had active skin surface warming with an upper body cover. The device was activated when core temperature decreased to less than 36 °C. The reduction in core temperature was 0.6 °C during the first hour after induction and 0.4 °C during the second hour in both groups. In the control group, core temperature continued to decrease until the end of surgery, whereas in the Bair-Hugger group, the reduction in core temperature stopped after 1 h of warming, and then rewarming began. At the end of surgery, core temperature in the Bair-Hugger group was similar to core temperature before induction, and was higher than core temperature in the control group ($P < 0.003$).(*Br. J. Anaesth.* 1996; **76**: 459–460)

Key words

Surgery, vascular. Equipment, warming devices. Monitoring, temperature. Temperature, monitoring. Hypothermia.

Intraoperative hypothermia is common during abdominal aortic surgery [1]. Forced air warming has been shown to be an efficient preventive method against hypothermia in a wide variety of surgical procedures [2–5]. In these studies, skin warming was started at the beginning of anaesthesia. After induction of anaesthesia for abdominal aortic surgery, insertion of i.v. cannulae, haemodynamic monitoring and subsequent surgical preparation delay warming for 1 h, while initial hypothermia induced by internal heat redistribution continues. The aims of this study were to evaluate the efficacy of forced air warming during abdominal aortic surgery when initial hypothermia had began.

Methods and results

In a prospective design, we studied 18 adult ASA II or III patients undergoing elective abdominal aortic surgery (aortic aneurysm repair or aortobifemoral bypass). None was obese, febrile or had a history of endocrine disease. Two hours before surgery, patients received preoperative cardiovascular treatment orally and morphine 0.1 mg kg^{-1} i.m. Anaesthesia was induced with flunitrazepam 0.03 mg kg^{-1} and fentanyl 5 μg kg^{-1} i.v.; pancuronium 0.1 mg kg^{-1} was then administered and the trachea intubated. The lungs were ventilated via a semi-closed circle system, at a fresh gas flow of 1.5 litre min^{-1} to maintain end-tidal $P\text{CO}_2$ at 4.8–5.3 kPa. Anaesthesia was maintained with isoflurane and 50% nitrous oxide in oxygen, fentanyl 5 μg kg^{-1} h^{-1} and pancuronium. Core temperature (Tc) and haemodynamic state were monitored using a pulmonary artery catheter inserted before induction of anaesthesia. The operating room temperature was kept at 20–21 °C throughout surgery. All infused i.v. fluids were warmed (Fenwal). Patients were then allocated randomly to one of two groups. In nine patients a warm cotton sheet was placed over the upper chest and arms (control group (CG)). In the other nine patients the upper chest and arms (i.e. 24% of body surface area) were covered by an upper body forced air blower cover (model 520) attached to a Bair-Hugger model 500 (Augustine Medical, Eden Prairie, MN, USA) which was set on high (Bair-Hugger group (BHG)). The forced air blanket was covered by two cotton sheets. The warming system was activated as soon as Tc decreased to less than 36 °C. At the end of surgery, patients were transferred to the intensive care unit for continuous ventilation until complete recovery. Data were analysed with ANOVA and the Mann–Whitney U test. Differences were considered statistically significant when $P < 0.05$.

The two groups did not differ in age (mean 59 (range 42–79) yr in group CG *vs* 59 (43–79) yr in group BHG), mean duration of anaesthesia (366 (SD 53) min in group CG *vs* 400 (50) min in group BHG), duration of surgery (278 (54) min in group CG *vs* 312 (47) min in group BHG), end-tidal isoflurane concentration (0.6 (0.3)% in group CG *vs* 0.8 (0.2)% in group BHG), blood loss (0.4 (0.2) litre in group CG *vs* 0.8 (0.4) litre in group BHG), infused volume of solutions (3.1 (0.6) litre in group CG *vs* 3.8 (0.8) litre in group BHG) and operating room temperature (21 (0.5) °C in group CG *vs* 21 (0.7) °C in group BHG).

J. Karayan*, MD, D. Thomas, MD, L. Lacoste, MD, K. Dhoste, MD, J. Fusciardi, MD (Department of Anaesthesiology and Surgical Intensive Care); J. B. Ricco, MD (Department of Vascular Surgery); University Hospital, Poitiers, France.

Accepted for publication: November 10, 1995.

*Address for correspondence: Département d'Anesthésie-Réanimation, CHU Poitiers, 86021 Poitiers Cedex, France.

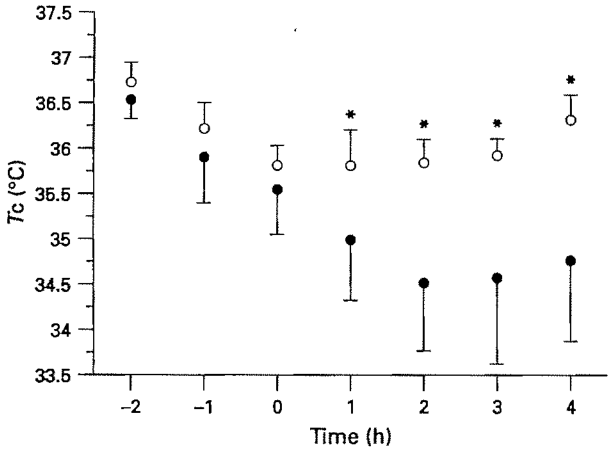


Figure 1 Intraoperative changes in core temperature (*T*c) (mean, SD) in the control (●) and Bair-Hugger (○) groups. Elapsed time zero (*T*0) identifies the beginning of rewarming in the Bair-Hugger group. *$P < 0.05$ *vs* control group.

Variations in *T*c for the patients are shown in figure 1. Before induction of anaesthesia there was no difference in mean *T*c between the groups (36.5 (SD 0.2) °C in group CG *vs* 36.7 (0.2) °C in group BHG). During the first hour after induction of anaesthesia, *T*c in both groups decreased (0.6 °C), and by the second hour a subsequent reduction of 0.4 °C had occurred. In group CG, *T*c continued to decrease until the end of the intervention (34.7 (1.0) °C). In group BHG, *T*c decreased to less than 36 °C (35.8 (0.2) °C) 2 h after induction. At this time the warming system was activated. One hour after the onset of active warming the reduction in temperature was stopped, and then the patients began to rewarm. During the subsequent course of the procedure, *T*c remained significantly higher in group BHG than in group CG ($P < 0.003$). *T*c in group BHG at the end of surgery was 36.5 (0.3) °C, that is similar to *T*c before induction.

Comment

All unwarmed patients were hypothermic at the end of surgery. In contrast, delayed forced air warming prevented intraoperative hypothermia.

Several authors have shown that the use of a limited skin surface is sufficient to prevent postoperative hypothermia [2–5], a finding confirmed by our study. However, in these studies skin warming was started just after induction of anaesthesia. The main purpose of our study was to show that delayed skin warming may be efficient during abdominal aortic surgery lasting more than 5 h.

A decrease in *T*c was observed during the first hour of anaesthesia in all patients. This initial hypothermia cannot be prevented, even if warming is started as soon as the patient is placed on the operating table [2]. In our study warming was started later, when *T*c decreased to less than 36 °C. There were several reasons for this delay in activating the warming system: first, the use of a warming system before induction would have required a cover on the lower limbs. In our opinion this seemed hazardous in patients with aortoiliac occlusive disease because of the risk of burning. Moreover, Beebe and colleagues showed that in pigs, warming of the hind legs during abdominal aortic surgery worsened the haemodynamic consequences of aortic declamping [6]. Second, putting the cover over the upper limbs would have avoided this risk, but insertion of invasive monitoring in the upper part of the body would have been precluded. Third, because of these two imperatives and in order to standardize the BHG group, we arbitrarily activated cutaneous warming at 36 °C.

Our study demonstrated that limited warming of the upper chest and arms was effective after the initial hypothermia by redistribution had started; it stopped the cooling and provided a normal *T*c at the end of the intervention. However, a minimum duration of 2 h is mandatory to start core warming, and 4 h of warming are needed to normalize *T*c.

Acknowledgements

We thank Dr A. Lienhart and Dr D. Sessler for helpful suggestions and criticisms of the manuscript.

References

1. Lewis DG, Mackenzie A. Cooling during major vascular surgery. *British Journal of Anaesthesia* 1972; **44**: 859–864.
2. Hynson JM, Sessler DI. Intraoperative warming therapies: a comparison of three devices. *Journal of Clinical Anesthesiology* 1992; 4: 194–199.
3. Kurz A, Kurz M, Poeschl G, Faryniak B, Redl G, Hackl W. Forced-air warming maintains intraoperative normothermia better than circulating-water mattresses. *Anesthesia and Analgesia* 1993; 77: 89–95.
4. Camus Y, Delva E, Just B, Lienhart A. Leg warming minimizes core hypothermia during abdominal surgery. *Anesthesia and Analgesia* 1993; 77: 995–999.
5. Bennett J, Ramachandra V, Webster J, Carli F. Prevention of hypothermia during hip surgery: effect of passive compared with active skin surface warming. *British Journal of Anaesthesia* 1994; 73: 180–183.
6. Beebe DS, Gauthier RL, DeMars JJ, Iaizzo PA. Lower extremity hypothermia is beneficial during infra-renal aortic cross-clamping in pigs. *Anesthesia and Analgesia* 1993; 77: 241–249.

British Journal of Anaesthesia 1996; 76: 461–463

Fentanyl increases intracellular Ca^{2+} concentrations in SH-SY5Y cells

A. L. WANDLESS, D. SMART AND D. G. LAMBERT

Summary

Classically, opioids inhibit Ca^{2+} influx, but recent reports suggest opioids may also stimulate Ca^{2+} entry. Therefore, we have measured the effect of opioids on intracellular Ca^{2+} ($[Ca^{2+}]_i$), fluorimetrically, in Fura-2-loaded SH-SY5Y cells. Fentanyl 0.3 μmol litre^{-1} caused a mean increase in $[Ca^{2+}]_i$ of 18.8 (SEM 2.1) nmol litre^{-1} in some (30.3%) batches of SH-SY5Y cells. In responding cells, the fentanyl-induced increase in $[Ca^{2+}]_i$ was dose-dependent, with an EC_{50} of 0.73 μmol litre^{-1}. This response was naloxone-reversible, and the δ opioid agonist [D-Pen^{2,5}]enkephalin had no effect on $[Ca^{2+}]_i$, suggesting the fentanyl-induced Ca^{2+} response was entirely mediated by the μ opioid receptor. Fentanyl 0.3 μmol litre^{-1} increased $[Ca^{2+}]_i$ without preactivation of phospholipase C by another agonist, and this was markedly reduced by Ni^{2+} 2.5 mmol litre^{-1}. These data suggest that μ opioids directly increase $[Ca^{2+}]_i$ by stimulating Ca^{2+} influx in SH-SY5Y cells. (*Br. J. Anaesth.* 1996; **76**: 461–463)

Key words

Analgesics opioid, fentanyl. Receptors, opioid. Model, neuroblastoma cells. Ions, calcium.

Classically, opioids inhibit Ca^{2+} entry via voltage-sensitive Ca^{2+} channels (VSCC), and this is generally accepted as part of the cellular basis for analgesia [1]. However, several recent reports have shown that opioids also stimulate Ca^{2+} influx [2]. Indeed, it has been proposed that opioid-induced increases in intracellular Ca^{2+} concentrations ($[Ca^{2+}]_i$) may be involved in the biochemical events underlying analgesia [3].

We have reported recently that μ, but not δ, opioids activate phospholipase C (PLC) in SH-SY5Y human neuroblastoma cells via a pertussis toxin-sensitive G-protein [1]. The subsequent increase in inositol(1,4,5)triphosphate ($Ins(1,4,5)P_3$) formation was abolished by removal of extracellular Ca^{2+} or by preincubation with nifedipine or (*R*+)Bay K8644 [1, 2], suggesting that μ opioids open L-type VSCC, thus allowing Ca^{2+} influx to activate PLC [2]. However, previous studies using SH-SY5Y cells failed to detect any opioid-induced increase in $[Ca^{2+}]_i$ unless PLC had been pre-activated by another agonist [4, 5]. Therefore, in the current investigation we have examined the effects of μ and δ opioids on $[Ca^{2+}]_i$, measured fluorimetrically in Fura-2-loaded cells, and report that μ opioids directly stimulate Ca^{2+} influx in SH-SY5Y cells.

Methods and results

SH-SY5Y (from Dr J. L. Biedler, passages 75–100) cells were maintained in minimum essential medium with Earle's salts and L-glutamine 2 mmol litre^{-1} supplemented with penicillin 100 u.ml^{-1}, streptomycin 100 μg ml^{-1}, fungizone 2.5 μg ml^{-1} and 10% fetal calf serum (Gibco, UK). Cells were harvested with HEPES-buffered saline 10 mmol litre^{-1}–0.02% EDTA, pH 7.4, washed twice with and resuspended in Krebs–HEPES buffer, pH 7.4, of the following composition (mmol litre^{-1}): Na^+ 143.3; K^+ 4.7; Ca^{2+} 2.5; Mg^{2+} 1.2; Cl^- 125.6; $H_2PO_4^-$ 1.2; SO_4^{2-} 1.2; glucose 11.7; and HEPES 10.

Each batch of cells was divided into 5–7 cuvettes and $[Ca^{2+}]_i$ was measured fluorimetrically in Fura-2-loaded whole cell populations in these cuvettes, as described previously [6]. Briefly, cells were incubated at 37 °C with Fura-2/AM 3 μmol litre^{-1} (Sigma, UK) for 30 min, washed and incubated at 20 °C for 20 min to allow complete ester hydrolysis. Some cells were preincubated with naloxone 1 μmol litre^{-1} at 20 °C for 5 min immediately before use. $[Ca^{2+}]_i$ was measured in 2-ml suspensions at 37 °C in a Perkin–Elmer LS50B spectrofluorimeter, using 340/380-nm excitation wavelengths, with emission at 510 nm. $[Ca^{2+}]_i$ was calculated from the 340/380 ratio as described previously [6], where Rmax and Rmin were determined with Triton-X (0.01%) and EGTA (4.5 mmol litre^{-1}, pH > 8.0), respectively. Changes of less than 5 nmol litre^{-1} were treated as 0.

Data are given as mean (SEM) or, where appropriate, as a representative trace of at least $n = 5$. EC_{50} values were obtained by computer-assisted curve fitting using Graphpad. Statistical comparisons were made where appropriate by ANOVA or Student's *t*-test, or both.

Fentanyl 0.3 μmol litre^{-1}, a μ-preferring opioid agonist [1], caused a naloxone-reversible increase (18.6 (2.2) nmol litre^{-1}) in $[Ca^{2+}]_i$ (fig. 1A) in some (30.3% from $n = 33$) batches of SH-SY5Y cells. It is

---

ANNA L. WANDLESS, BA (HONS), DARREN SMART, BSC (HONS), PHD, DAVID G. LAMBERT, BSC (HONS), PHD, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW.
Accepted for publication: October 26, 1995.
Correspondence to D.G.L.

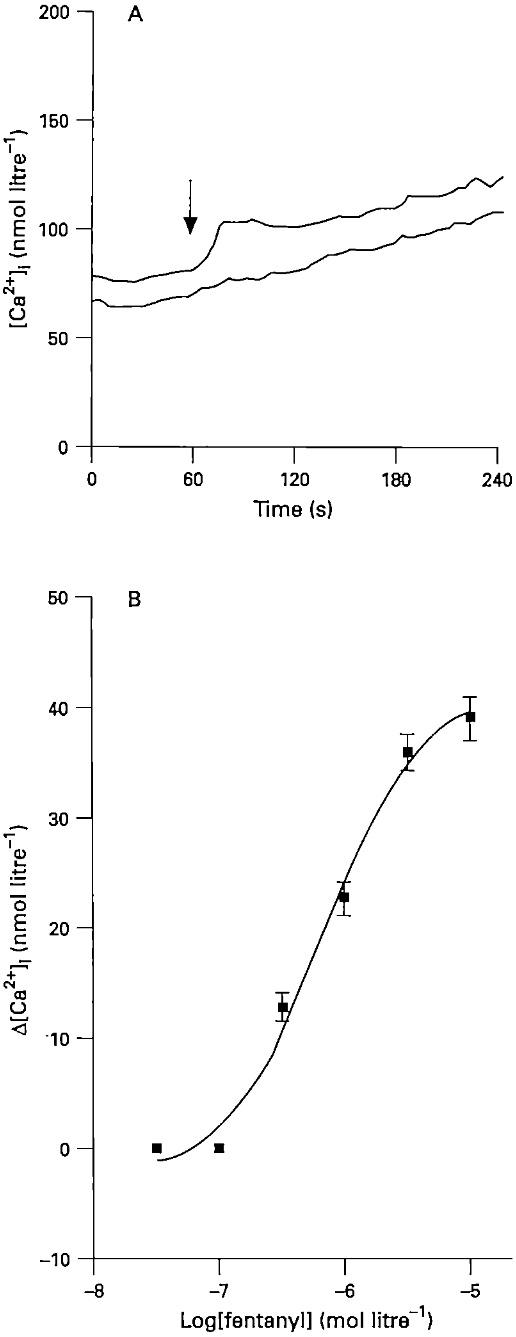


Figure 1 Time course (A) and dose-dependency (B) of the effect of fentanyl on $[Ca^{2+}]_i$ in SH-SY5Y cells. Cells were loaded with the Ca^{2+}-indicator dye Fura-2, and $[Ca^{2+}]_i$ measured by fluorimetry before and after the addition (indicated by arrow) of fentanyl 30 nmol litre^{-1}–10 μmol litre^{-1}. A: Lower trace is in the presence of naloxone 1 μmol litre^{-1} (data are representative of $n = 5$). (B) Data are mean, SEM (n = 5–8). SH-SY5Y dose–response curve was $P < 0.05$ by ANOVA.

worth noting that all samples (i.e. cuvettes) from the same batch of cells responded in the same way, and that the non-responders had normal Ca^{2+} responses to carbachol (data not shown). In responding cells, the response was dose-dependent (fig. 1B), with an EC_{50} of 0.73 μmol litre^{-1}. Preincubation with Ni^{2+} 2.5 mmol litre^{-1} markedly reduced the fentanyl (0.3 μmol litre^{-1})-induced increase in $[Ca^{2+}]_i$ (from 18.8 (2.1) to 7.0 (2.8) nmol litre^{-1}), indicating that the response was caused by Ca^{2+} influx. The δ opioid agonist DPDPE (1 μmol litre^{-1}) had no effect on $[Ca^{2+}]_i$ in SH-SY5Y cells (data not shown), even if PLC had been pre-activated with carbachol 50 μmol litre^{-1}, contrary to previous reports [4, 5]. This suggests that the opioid-induced Ca^{2+} response in SH-SY5Y cells could be μ-specific, and is in agreement with the evidence that μ, but not δ, opioids stimulate Ins(1,4,5)P_3 formation in these cells [1]. However, full pharmacological characterization of the Ca^{2+} response to fentanyl was not possible because of the small size and variability of occurrence of the response.

Comment

We have shown that μ opioids cause a dose-dependent increase in $[Ca^{2+}]_i$ in SH-SY5Y cells, and that this response does not require pre-activation of PLC with another agonist. Earlier studies using SH-SY5Y cells failed to detect any such changes [4, 5]. However, there is indirect evidence that μ opioids stimulate Ca^{2+} influx in SH-SY5Y cells, as block of Ca^{2+} entry with Ni^{2+} or nifedipine abolished μ opioid-induced Ins(1,4,5)P_3 formation in these cells [1, 2]. Opioid-induced increases in $[Ca^{2+}]_i$, and the subsequent stimulation of K^+ channel activity, has been suggested as one of the cellular mechanisms underlying analgesia [3]. Indeed, we have previously reported data suggesting that μ opioids increase Ca^{2+}-activated K^+ channel activity in SH-SY5Y cells [2]. Alternatively, there is evidence linking opioid-induced increases in $[Ca^{2+}]_i$ to the development of tolerance [2].

It has been proposed that opioids can only increase $[Ca^{2+}]_i$ in SH-SY5Y cells if the cell has been "primed" by prior activation of PLC [4, 5]. However, we have clearly demonstrated that opioids can increase $[Ca^{2+}]_i$ without pre-activation of PLC in this cell type. Moreover, even when we pre-activated PLC in SH-SY5Y cells with carbachol, DPDPE did not increase $[Ca^{2+}]_i$, contrary to previous reports [4, 5]. This suggests that this clonal cell-line may not be as homogeneous as previously thought, particularly as in the present study only 30.3% of the batches of cells responded. Alternatively, these discrepancies may reflect the effects of different cell culture regimens.

We have proposed previously that μ, but not δ, opioids stimulate Ins(1,4,5)P_3 formation in SH-SY5Y cells by opening L-type VSCC and so allowing Ca^{2+} influx to activate PLC [2]. In the current investigation we found that μ, but not δ opioids stimulated Ca^{2+} influx in SH-SY5Y cells, which supports this hypothesis. However, comparison of the dose–response curves for these two responses, with EC_{50} values of 16 and 730 nmol litre^{-1} for opioid-induced Ins(1,4,5)P_3 formation [1] and increased $[Ca^{2+}]_i$, respectively, indicates that the two phenomena may not be causally related. However, large, localized increases in $[Ca^{2+}]_i$ in the vicinity of the plasma membrane could still activate membrane-bound PLC, yet would be underestimated, or even missed entirely, using measurements of $[Ca^{2+}]_i$ in whole cell populations. Therefore, further studies using subcellular fluorescence imaging are necessary to test our hypothesis.

In conclusion, we report here for the first time that μ opioids increase [Ca^{2+}]$_i$ by stimulating Ca^{2+} influx in SH-SY5Y cells, and that this response does not require "priming" of the cell by prior activation of PLC with another agonist.

Acknowledgement

Financial support from the Wellcome Trust is gratefully acknowledged. A. L. Wandless was a Wellcome Trust vacation student.

References

1. Smart D, Smith G, Lambert DG. μ-Opioid receptor stimulation of inositol(1,4,5)trisphosphate formation via a pertussis toxin-sensitive G protein. *Journal of Neurochemistry* 1994; **62**: 1009–1014.
2. Smart D, Lambert DG. Desensitization of the μ-opioid activation of phospholipase C in SH-SY5Y cells: the role of protein kinases C and A, and Ca^{2+}-activated K^+ currents. *British Journal of Pharmacology* 1995; **116**: 2655–2660.
3. Lipp J. Possible mechanisms of morphine analgesia. *Clinical Neuropharmacology* 1991; **14**: 131–147.
4. Connor MA, Henderson G. Opioids mobilize intracellular calcium in SH-SY5Y cells. *British Journal of Pharmacology* 1994; **113**: 16P.
5. Connor MA, Planner A, Henderson G. δ and μ opioid receptor mobilization of intracellular calcium in neuroblastoma cells. *Regulatory Peptides* 1994; **54**: 65–66.
6. Smart D, Wandless AL, Lambert DG. Activation of phospholipase C in SH-SY5Y neuroblastoma cells by potassium-induced calcium entry. *British Journal of Pharmacology* 1995; **116**: 1797–1800.

British Journal of Anaesthesia 1996; **76**: 464–466

CASE REPORTS

Myocardial ischaemia associated with Ehlers–Danlos syndrome

C. M. PRICE, S. FORD, L. ST JOHN JONES AND V. MURDAY

Summary

A 38-yr-old man with an unusual type of Ehlers–Danlos syndrome presented for elective abdominal aortic aneurysm repair. During surgery he developed acute myocardial ischaemia, resulting in abandonment of the procedure. He was shown subsequently to have severe triple vessel coronary artery disease. Silent ischaemia associated with severe coronary artery disease, although rare, may be associated with the syndrome and is difficult to recognize as other cardiac abnormalities are frequently present. (*Br. J. Anaesth.* 1996; **76**: 464–466)

Key words

Ehlers–Danlos syndrome. Surgery, aneurysm. Heart, ischaemia. Complications, Ehlers–Danlos syndrome.

Ehlers–Danlos syndrome is a heterogeneous group of connective tissue disorders. It was described by Ehlers in 1899 and by Danlos in 1908. Its main features are articular hyperlaxicity, cutaneous hyperelasticity, vascular fragility and cutaneous fragility [1]. These features present the anaesthetist with potential problems and hazards. Many different types are classified on clinical criteria. However, the majority of patients do not fit neatly into any of the types. Recent developments in understanding the molecular structure of collagen have further confused the issue with the finding that similar abnormalities of the same type of collagen can produce varying phenotypes of Ehlers–Danlos syndrome or osteogenesis imperfecta. Although all Ehlers–Danlos syndrome types may present problems for the anaesthetist, it is type IV which poses the greatest problems and has been the subject of previous case reports [2–4]. Type IV is usually associated with abnormalities of type III collagen. Sufferers may have friable arteries which can rupture spontaneously causing sudden death.

We report a case of a young, apparently healthy man, who had an unspecified type of Ehlers–Danlos syndrome, with type 1 collagen abnormality. He developed acute, severe myocardial ischaemia during operation for elective aortic aneurysm repair. Emergency coronary artery bypass grafting was subsequently performed. To our knowledge this is the first case report of myocardial ischaemia occurring during anaesthesia that is specifically associated with Ehlers–Danlos syndrome.

Case report

A 38-yr-old man presented for elective abdominal aortic aneurysm repair. The aneurysm, measuring 7 cm, was discovered after x-ray of his lumbar spine. In the past he had undergone repair of a patent ductus arteriosus at 3 yr of age and was routinely followed-up by various cardiologists. When aged 13 yr he was found to have mild supravalvular pulmonary stenosis and was investigated for chest discomfort after cycling when aged 28 yr. An echocardiogram at that time revealed aortic regurgitation and mild left ventricular hypertrophy. He remained well and continued to have a yearly cardiology review, including an echocardiogram. Mild deterioration in left ventricular function was noted on echocardiogram 2 yr before this procedure for which he was commenced on enalapril. His exercise tolerance was good and he continued to cycle 5–10 miles a day until his aneurysm was discovered.

He was seen before operation by a cardiologist. On examination, he was noted to be of short stature with some dysmorphic features. His skin was velvety soft and he had absent earlobes. He had moderate kyphoscoliosis, flat feet and hypermobile joints, but no scarring. Para-umbilical and inguinal herniae were noted. Cardiovascular examination revealed murmur of aortic regurgitation, pulse in sinus rhythm with an arterial pressure of 120/60 mm Hg. Haematological and biochemical investigations, including clotting studies, were all normal. Chest x-ray was unremarkable. The electrocardiogram (ECG) showed prolonged QRS complexes, left ventricular hypertrophy and Q-waves in the inferolateral leads. These changes had all been present for the past decade and were thought to relate to his congenital heart defects and cardiac surgery. Echocardiographic findings were of moderate aortic regurgitation with an aortic root measurement of 4 cm, normal end-diastolic volume and mild impairment of systolic function. Ultrasound scan of his abdomen revealed a 7.2-cm infrarenal aneurysm extending to the bifurcation. The cardiologist also felt that he had

---

C. M. PRICE*, DCH, FRCA, S. FORD†, FRCA, L. ST JOHN JONES, FRCA, Crawley Hospital, Crawley, West Sussex. V. MURDAY, MRCP, St George's Hospital, London. Accepted for publication: October 27, 1995.

Present addresses:
*Queen Alexandra Hospital, Cosham, Portsmouth.
†St George's Hospital, London.

dysmorphic features suggestive of Ehlers–Danlos syndrome and so referred him for a genetic examination. Although there was no family history of Ehlers–Danlos syndrome, his parents were noted to be first cousins. In the absence of any history of excessive bleeding, bruising or scarring, the provisional genetic opinion was that he had type VI Ehlers–Danlos syndrome, as opposed to the more common types I or IV.

Before operation it was felt that, in view of his congenital heart disease, he would benefit from pulmonary artery (PA) catheterization. He was therefore admitted to the intensive care unit. A PA catheter was inserted without difficulty. Measurements revealed cardiac output of a 4.7 litre min^{-1} with a pulmonary capillary wedge pressure of 12 mm Hg. In theatre a radial artery cannula was inserted, also without difficulty. Monitoring was then started and included an ECG in the CM5 configuration, pulse oximetry, direct arterial pressure and pulmonary artery pressure. His lungs were then preoxygenated and anaesthesia was induced with propofol 140 mg, fentanyl 150 μg and vecuronium 10 mg. Laryngoscopy revealed a grade 3 larynx necessitating intubation with the aid of a gum elastic bougie. An extradural catheter was inserted at L1–2. Sensation during insertion was found to be strange because of the abnormal feel of the ligaments. He was given Gelofusine 500 ml and a test dose of 0.5 % bupivacaine 3 ml without incident. This was followed by 0.5 % bupivacaine 7 ml and diamorphine 2.5 mg, given in incremental doses. His arterial pressure remained stable. The operation proceeded uneventfully until, during mobilization of the aneurysm, he developed marked ST segment elevation on the ECG which rapidly progressed to a supraventricular tachycardia, followed by ventricular tachycardia. His arterial pressure then decreased to 55/40 mm Hg. He required DC cardioversion of 50, 100 and then 200 J to restore sinus rhythm. Before this there was no episode of hypotension. However, after restoration of sinus rhythm he had an intermittent sinus tachycardia of 130 beat min^{-1} accompanied by hypotension and the procedure was therefore abandoned. These episodes were short-lived, not requiring further treatment. During the next 30 min, cardiovascular stability improved, ST segment on the ECG returned to normal and he did not require further treatment. He was transferred to the intensive care unit where a 12-lead ECG was performed. This showed no change from his previous ECG and an echocardiogram showed no deterioration from preoperative function.

He was sedated and his lungs ventilated overnight in intensive care and he remained stable. The following day attempts were therefore made to wean him, but this resulted in the return of marked tachycardia with accompanying ST segment elevation. Weaning was stopped and transfer to the regional cardiothoracic unit was arranged.

Cardiac catheterization revealed the presence of severe generalized triple vessel disease. He underwent coronary artery bypass grafting the following day without any further attempts to wean him. The aorta was noted to be extremely friable. He was stable throughout the procedure. He underwent an uneventful abdominal aneurysm repair 1 week later. Skin biopsy was taken for fibroblast culture and collagen studies.

Discussion

Ehlers–Danlos syndrome has a complicated, multifaceted presentation. Our patient was felt to have type VI Ehlers–Danlos syndrome, caused by lysyl oxidase deficiency on the basis of a likely recessive inheritance, the presence of scoliosis, scarring and the absence of bruising [5]. However, collagen studies did not confirm this and were more consistent with a type I collagen abnormality. This is associated more commonly with osteogenesis imperfecta although it has been reported in association with type VII Ehlers–Danlos syndrome [6]. Our patient did not fit neatly into any category. Indeed, the immense heterogeneity of the collagen diseases and improved detection of the genetic defects involved are likely to lead to re-classification of collagen disorders on the basis of the actual defective gene in the future.

Anaesthetic problems in Ehlers–Danlos syndrome were reviewed extensively by Dolan, Sisko and Riley [2]. Problems may occur in all types because of lax, unstable joints, abnormal skin elasticity and friable vessels. These lead to difficulty with tracheal intubation and insertion of cannulae or catheters. Abnormal vessel walls and platelet defects may lead to uncontrollable haemorrhage [7]. There may also be lung cysts present, increasing the risk of pneumothorax [9]. Dolan, Sisko and Riley did not recommend the use of extradural analgesia because of the risk of haematoma, but since then two authors have described its successful use in obstetric anaesthesia [3, 4]. We felt that extradural anaesthesia was appropriate in our patient. Extradural block is used routinely in many centres for aortic aneurysm repair as it provides excellent analgesia, reducing anaesthetic requirements during operation. After operation, pain may lead to increased oxygen requirement thus increasing the risk of myocardial ischaemia. Extradural analgesia reduces this risk compared with systemic opioids [9]. In aortic insufficiency an increase in afterload caused by pain may worsen regurgitation, with the risk of acute left ventricular volume overload [10]. Extradural analgesia may prevent this or actually decrease afterload. The extradural catheter was inserted under controlled conditions by an experienced operator with incremental doses of local anaesthetic accompanied by monitoring of pulmonary artery wedge pressure. Tachycardia, arrhythmia and hypotension occurred 1 h after the last dose of bupivacaine and we felt therefore that his problems were unrelated to the effects of the extradural.

Cardiac complications are a recognized feature of Ehlers–Danlos syndrome [11]. The main problems are: (a) valvular diseases—regurgitation or prolapse caused by abnormal valve structure; (b) congenital heart disease—atrioventricular septal defects, tetralogy of Fallot and dextrocardia; (c) conduction defects—atrioventricular block, incomplete right bundle branch block and extrasystoles.

Coronary artery disease occurring in association with Ehlers–Danlos syndrome has been reported [11]. Both cases were in type IV disease and led to myocardial infarction. All cases, including our own, had age ranges in their thirties. Neither of the cases reported had symptoms of angina pectoris before their myocardial infarction. It seems likely that fragility and friability of the coronary arteries leading to plaque formation may be implicated. In our patient ischaemia was related to handling of the aneurysm and later attempts to wean him. He did not develop myocardial infarction.

Because of the many cardiac defects seen in Ehlers–Danlos syndrome, ECG recordings are likely to be abnormal, making the detection of ischaemia more difficult. Cardiac catheterization has been described as hazardous in Ehlers–Danlos syndrome as the friable arteries make haemorrhage from the entry site likely [9]. Exercise or dipyridamole thallium scanning has been recommended for certain at risk candidates undergoing aortic aneurysm repair. It would perhaps be a suitable screening measure in Ehlers–Danlos syndrome sufferers before undertaking a major procedure.

In summary, the anaesthetic implications of Ehlers–Danlos syndrome are multiple. Before surgery, the help of a geneticist is useful to characterize the type of Ehlers–Danlos syndrome presenting so that a more accurate prediction can be made of the problems likely to occur. Myocardial ischaemia, although rare, can occur in young sufferers of Ehlers–Danlos syndrome without prior symptoms. This makes diagnosis difficult, especially if associated with other congenital abnormalities. This possibility should, however, be borne in mind and the appropriate investigations, such as thallium scanning, performed.

References

1. Pope FM. Ehlers Danlos syndrome. In: *Baillière's Clinical Rheumatology, vol.* 2 (London: Baillière Tindall, 1991; 321–349.
2. Dolan P, Sisko F, Riley E. Anesthetic considerations for Ehlers Danlos syndrome. *Anesthesiology* 1980; **52**: 266–269.
3. Brighouse D, Guard B. Anaesthesia for Caesarean section in a patient with Ehlers Danlos syndrome type IV. *British Journal of Anaesthesia* 1992; **69**: 517–519.
4. Abouleish E. Obstetric anaesthesia and Ehlers Danlos syndrome. *British Journal of Anaesthesia* 1980; **52**: 1283–1285.
5. Wenstrup RJ, Murad S, Pinnell SR. Ehlers Danlos syndrome type VI. *Journal of Pediatrics* 1989; **115(3)**: 405–409.
6. Sasaki T, Arai K, Ono M, Yamaguchi T, Furuta S, Nagai Y. EDS: a variant characterised by the deficiency of pro alpha 2 chain type I procollagen. *Archives of Dermatology* 1987; **123**: 76–79.
7. Anstey A, Mayne K, Winter M, Van der Pette J, Pope FM. Platelet and coagulation studies in Ehlers Danlos syndrome. *British Journal of Dermatology* 1991; **125**: 155–163.
8. Corrin B, Simpson CGB, Fisher C. Fibrous pseudotumours and cyst formation in the lungs with Ehlers Danlos syndrome. *Histopathology* 1990; **17**: 478–479.
9. Liu S, Randall L, Neal JM. Epidural anesthesia and analgesia—their role in post-operative outcome. *Anesthesiology* 1995; **82**: 1474–1501.
10. Chestnut DH, ed. Valvular disorders. In: *Obstetric Anesthesia, Principles and Practice.* Chicago: Mosby Year Book Inc 1994; **40**: 755–763.
11. Kitazono T, Imayama S, Takeshita A, Nakamura M. Two cases of myocardial infarction in type IV Ehlers Danlos syndrome. *Chest* 1989; **95**: 1274–1277.

British Journal of Anaesthesia 1996; 76: 467–469

Reducing the potential morbidity of an unintentional spinal anaesthetic by aspirating cerebrospinal fluid

P. SOUTHORN, G. M. S. VASDEV, R. C. CHANTIGIAN AND G. M. LAWSON

Summary

We describe two cases where we attempted to reduce the adverse effects of inadvertent spinal anaesthesia by aspirating local anaesthetic-contaminated cerebrospinal fluid (CSF). Analysis of this CSF for its local anaesthetic concentration revealed that we were able to recover 51 % and 39 % of the administered lignocaine. It is suggested that such aspiration may be a helpful additional measure to the supportive management of this complication. (*Br. J. Anaesth.* 1996; **76**: 467–469)

Key words

Anaesthetic techniques, extradural. Cerebrospinal fluid. Complications, morbidity.

Injection of an appropriate dose of local anaesthetic for extradural anaesthesia into an extradural catheter which has perforated the dura mater may result in total spinal anaesthesia. On the last two occasions when this complication occurred in our institution, we immediately aspirated contaminated cerebrospinal fluid (CSF), in an attempt to reduce the height of the block. Because our patients did not develop total spinal anaesthesia and analysis of the aspirated CSF showed that significant amounts of injected local anaesthetic could be recovered by this means, we suggest that such aspiration may be a helpful adjunct to the conventional supportive management of patients in this situation.

Case report

PATIENT NO. 1

An extradural anaesthetic was planned for a repeat elective Caesarean section in a 28-yr-old healthy woman with a contracted pelvis and unstable fetal lie. With the patient in the left lateral position, the extradural space at L3–4 was identified with an extradural needle using the loss of resistance to saline technique. An extradural catheter was advanced 4 cm through this needle and aspiration was negative for CSF or blood. After the patient had been placed in the supine position with left uterine displacement and the i.v. fluid bolus had been completed, a test dose of 2 % lignocaine 3 ml with adrenaline 1:200000 was injected into the extradural catheter. This produced no sensory or motor block and no change in the patient's heart rate, as monitored by an electrocardiogram and pulse oximeter, over the course of the next 4 min. Subsequently, 2 % lignocaine 7 ml with adrenaline 1:200000 and fentanyl 10 $\mu g\ ml^{-1}$ were injected through the catheter. Within 4–5 min, the patient stated that her legs had become completely numb and simultaneously her arterial pressure decreased from 120/80 to 70/50 mm Hg. Aspiration now revealed free-flowing CSF. A total of 20 ml of CSF was withdrawn over 40 s and sent in a glass bottle to the laboratory for analysis of lignocaine and fentanyl content.

Simultaneously, the patient's hypotension was managed by exaggerating left uterine displacement, placing the patient in the Trendelenburg position, giving an additional i.v. fluid bolus and repeated i.v. injections of ephedrine 5 mg (35 mg in total). Oxygen had been administered continuously via a face mask since insertion of the extradural catheter. The patient's arterial pressure stabilized at 110/70 mm Hg, she did not lose consciousness, her ventilatory frequency and laryngeal reflexes were normal and the fetal heart rate monitor revealed no evidence of fetal distress. On questioning, the patient complained that her arms felt heavier than usual but she had no demonstrable muscle weakness in either arm. By temperature discrimination, the spinal anaesthetic had extended to the C3–4 level.

Thirty-six minutes after the initial test dose of local anaesthetic, a 3650-g male infant was delivered, with Apgar scores of 7 and 8 at 1 and 5 min, respectively. After operation the catheter was removed intact and 3.75 h after receiving the local anaesthetic, the block had completely worn off. The patient had an uneventful postoperative course and did not develop a post-dural puncture headache.

PATIENT NO. 2

Extradural anaesthesia was planned for a 68-yr-old woman who was to undergo right total hip arthroplasty. With the patient lying on her side, the extradural space between L2–3 was identified with an extradural needle using the loss of resistance to saline technique. An extradural catheter was passed

---

PETER SOUTHORN, BSC, MB, BS, FRCA, GARY M. S. VASDEV, MB, BS, FRCA, ROBERT C. CHANTIGIAN, MD (Department of Anesthesiology); GEORGE M. LAWSON, PHD (Department of Laboratory Medicine); Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN 55905, USA. Accepted for publication: October 17, 1995.

Correspondence to P. S.

easily through this needle and aspiration of the latter was negative for CSF and blood. A test dose of 2% lignocaine 3 ml with adrenaline 1:200000 injected through the catheter produced no sensory or motor block and no change in heart rate, as monitored by an electrocardiogram and pulse oximeter after 3 min. In the subsequent 3 min, 2% lignocaine, 17 ml with adrenaline 1:200000 was injected incrementally through the catheter. Eleven minutes later, arterial pressure decreased from 150/80 to 94/40 mm Hg. This was treated promptly with ephedrine 10 mg i.v., an i.v. fluid bolus of 500 ml and her arterial pressure stabilized at 120/70 mm Hg.

Eighteen minutes after local anaesthetic administration, the patient could not move her hands and by sensory discrimination the level of block was at C5–6. Aspiration of the extradural catheter at this time revealed free flowing CSF and 30 ml was removed, placed in a glass bottle and sent to the laboratory for lignocaine assay. Ten minutes later she started recovering the use of her hands. Shortly afterwards, surgery commenced. Eighty-six minutes after the initial administration of lignocaine, the patient complained of some minor discomfort at the site of surgery. To treat this, 0.5% bupivacaine 1 ml was injected intrathecally through the catheter. A second 1 ml of 0.5% isobaric bupivacaine was administered 31 min later. This allowed surgery to be completed without discomfort. At the end of surgery, the extradural catheter was removed intact. The patient had an uneventful postoperative course and did not develop a post-dural puncture headache.

LIGNOCAINE AND FENTANYL ASSAY

Lignocaine concentration in CSF was measured by an enzyme multiplied immunoassay technique (EMIT) using calibrators and reagents obtained from Syva Company (San Jose, CA, USA) adapted to a Monarch automated chemistry analyser (Instrumentation Laboratory, Lexington, MA, USA). The assay, used routinely to measure lignocaine concentration in serum, was validated for use on CSF by assaying lignocaine standards of known concentration prepared by dissolving pure lignocaine in a solution designed to mimic the electrolyte composition, osmolality and pH of normal CSF. Percentage recovery (mean (SD)) at three concentrations spanning the assay linear range was 97.6 (7.1)%. Fentanyl was extracted from CSF with chloroform:ethylacetate (80:20, v:v), and the organic phase was dried down under nitrogen. The residue was resuspended in methanol 100 μl and assayed for fentanyl by gas chromatography–mass spectrometry using a Hewlett-Packard (Palo Alto, CA, USA) 5980/5987 instrument. Deuterated fentanyl was added to CSF as an internal standard to correct for losses incurred during extraction and chromatography.

Discussion

The results are summarized in table 1. In the two patients, we recovered 51% and 39% of lignocaine administered intrathecally. Although definite conclusions cannot be drawn based on findings in two patients, the success in retrieving lignocaine combined with the lack of signs and symptoms of total spinal anaesthesia suggest that such CSF aspiration may be beneficial.

Table 1 Lignocaine and fentanyl recovery by CSF aspiration

	Patient No. 1	Patient No. 2
Total dose lignocaine injected (mg)	200	400
Volume of CSF removed (ml)	20	30
Concentration of lignocaine in CSF recovered (mg ml^{-1})	5.1	5.2
Total amount of lignocaine recovered		
mg	102	156
Percentage as injected	51	39
Total dose fentanyl injected (μg)	70	—
Concentration of fentanyl in CSF recovered (μg ml^{-1})	0.16	—
Percentage fentanyl recovered	4.7	—

Withdrawal of CSF to control the level of continuous spinal anaesthesia was described in 1948 [1]. Contaminated CSF removal as part of the management of an inadvertent spinal anaesthetic was suggested originally in a 1980 editorial [2]. We believe this report is the first to support this suggestion. Such CSF aspiration has been used routinely to attempt to overcome the potentially fatal consequences resulting from inadvertent excess intrathecal methotrexate [3–5]. It has also been used to treat intrathecal morphine overdose [6].

In addition to the need for more patient-based data, several other questions need to be addressed before CSF aspiration is incorporated routinely in the treatment of inadvertent spinal anaesthesia. Pharmacokinetic principles have been used to predict the percentage of intrathecally injected methotrexate removed by different volumes of CSF aspiration when performed at various time intervals after drug administration [3]. We aspirated 20 ml of CSF in our first patient and 30 ml in the second.The ideal volume of CSF to be recovered in this clinical situation remains to be resolved. Presumably removal of larger volumes than we used is more likely to result in post-dural puncture headache. The immediacy of such aspirations to maximize recovery of drug may also be important. This report does not suggest how much time may elapse from injection of local anaesthetic before this manoeuvre loses its clinical benefit. Drug recovery also depends on drugs diffusibility and lipid solubility [7]. This is illustrated by patient No. 1 in whom we recovered 51% of the administered lignocaine, but were only able to retrieve 4.7% of the concomitantly administered fentanyl.

References

1. Lemon WT, Paschal GW jr. Continuous–serial, fractional, controllable, intermittent–spinal anesthesia: With observation of 1000 cases. *Surgery, Gynecology and Obstetrics* 1942; 74: 948–956.
2. Covino BG, Marx GF, Finster M, Zsigmond EK. Editorial.

Prolonged sensory/motor deficits following inadvertent spinal anesthesia. *Anesthesia and Analgesia* 1980; **59**: 399–400.

3. Addiego JE jr, Ridgway D, Bleyer WA. The acute management of intrathecal methotrexate overdose: Pharmacologic rationale and guidelines. *Journal of Pediatrics* 1981; **98**: 825–828.
4. Ettinger LJ. Pharmacokinetics and biochemical effects of a fatal intrathecal methotrexate overdose. *Cancer* 1982; **50**: 444–450.
5. Jakobson AM, Kreuger A, Martinez O, Mortimer O, Henningsson S, Seidal H, Moe PJ. Cerebrospinal fluid exchange after intrathecal methotrexate overdose. A report of two cases. *Acta Paediatrica* 1992; **81**: 359–361.
6. Kaiser KG, Bainton CR. Treatment of intrathecal morphine overdose by aspiration of cerebrospinal fluid. *Anesthesia and Analgesia* 1987; **66**: 475–477.
7. de Jong RH. *Local Anesthetics*. St Louis, MO: Mosby Year Book, Inc., 1994.

British Journal of Anaesthesia 1996; **76**: 470

COMMENTARY

Consensus statement on autologous transfusion

PROCEEDINGS OF A CONSENSUS CONFERENCE HELD BY THE ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH, OCTOBER 4–6, 1995

People of the UK have been and continue to be well served by their National Blood Transfusion Services. The panel emphasized the need to utilize good surgical techniques which minimize blood loss and recognized the importance of efforts to limit the use of blood to clinical necessity.

Notwithstanding the safety of allogeneic blood transfusion, several questions have been raised internationally, particularly in North America and the European Union, suggesting that the supply of blood can be supplemented by autologous transfusion techniques. It is recognized that all blood transfusions carry risks. Screening of donated blood, however, has greatly reduced the potential risks of transfusion-transmitted diseases. There remains a degree of uncertainty on the immunological effects of allogeneic transfusion. When used as the sole source of transfused blood, the principal advantage of autologous blood transfusion is the avoidance of the risks of transmitting infectious agents and the potential immunological side effects of allogeneic transfused blood.

The panel noted the paucity of controlled, randomized trials in the evaluation of these procedures and recognized the need to develop appropriate methodology and outcome measures to determine risk benefit and cost effectiveness. Provision of services, present and future, should take account of the rights, interests and requirements of patients. Good medical practice requires disclosure of alternatives in addition to risks and benefits.

Preoperative autologous donation (PAD)

At the present time, in the UK, there is a low degree of public interest, although the facility of PAD is potentially widely available. In centres which offer this facility, the present take-up is low compared with a take-up rate in America of up to 10%, accounting for 5% of total blood usage. Not all patients are suitable and patients must be selected carefully on medical grounds. Eligible patients who undergo elective orthopaedic surgery are the primary targets of PAD and it is possible to achieve exclusive use of autologous blood in at least 75% of cases.

A current disadvantage is the difficulty of guaranteeing non-cancellation of routine surgery within the NHS. Other disadvantages include the possibility of cardiovascular accidents after donation. A further concern is that the operation has to be scheduled to allow for usually 1–4 donations at approximately weekly intervals. In some patients this could be a disadvantage. Although there are practical difficulties associated with the general introduction of PAD in the UK, we foresee that this practice may become more widespread provided that appropriate resources are made available.

Acute normovolaemic haemodilution (ANH)

The evidence presented suggests that when used alone, ANH has a limited capability for preventing the need for allogeneic blood. We acknowledge that there are potential benefits and hazards, and that careful evaluation of this technique is essential before it can be recommended for widespread use.

Intraoperative salvage (IS)

The clinical benefits of IS become more apparent in surgical procedures with acute blood loss of more than 1000 ml. Blood loss levels below this volume would not support the use of IS, particularly with respect to cost benefit. Provided that a rigid standard operating procedure is in place and the equipment is easily available with appropriate staff training, the side effects of IS are fewer than those associated with allogeneic transfusion. An increasing body of evidence indicates that this procedure can substantially reduce the need for allogeneic blood.

Future directions

Further work in the development of appropriate blood substitutes and agents to enhance haemostasis will help to reduce the need for allogeneic transfusion. We would also favour the establishment of a national register of adverse events relating to all autologous transfusion procedures.

British Journal of Anaesthesia 1996; **76**: 471–476

CORRESPONDENCE

Histamine release by neuromuscular blocking agents

Sir,—The design of the study by Naguib and colleagues [1] on the histamine releasing potencies of various neuromuscular blocking drugs resulted in cardiovascular changes which were profound, adverse and predictable. For example, the data sheet for mivacurium suggests administration over 5–15 s. The authors chose 5 s, despite quoting references which showed potential adverse haemodynamic changes caused by rapid administration of some benzylisoquinolinium neuromuscular blockers. Three minutes after administration of mivacurium, the control mean arterial pressure (MAP) of 76.0 mm Hg had decreased to a mean of 58.1 mm Hg, 2 SD below which gives an MAP of 43.7 mm Hg. Hypotension and tachycardia represents the worst possible combination of cardiovascular variables for myocardial perfusion, already compromised by covert coronary atherosclerosis at 60 yr of age, the maximum age in the study sample.

D. B. Todd
Department of Anaesthesia
Frenchay Hospital
Bristol

1. Naguib M, Samarkandi AH, Bakhamees HS, Magboul MA, El-Bakry AK. Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine. *British Journal of Anaesthesia* 1995; 75: 588–592.

Sir,—The design of our study [1] was not different from that of similar studies. For example, Basta and colleagues [2] and Moss and colleagues [3] administered atracurium and dimethyltubocurarine and tubocurarine, respectively, as a single rapid (5 s) bolus. Administration of mivacurium over 5 s is still within the recommendations of the manufacturer. However, slower administration of larger doses of benzylisoquinolinium compounds such as mivacurium 0.25 mg kg^{-1}, for example over 60 s, results in no significant changes in histamine concentrations or haemodynamic variables [4]. Therefore, with slower administration, the inherent differences between the neuromuscular blocking drugs studied could not have been elicited.

The dramatic scenario created by Dr Todd in his letter does not match our data. The patients in the mivacurium group were aged 20–41 (mean 28.4) yr. The ranges of mean arterial pressure and heart rate observed in this group were, respectively, 47–70 mm Hg and 76–93 beat min^{-1}. For those patients who may be compromised cardiovascularly, it is clear that selecting a drug with less histamine release may be an appropriate choice.

M. Naguib
University Department of Anaesthesia
King Khalid University Hospital
Riyadh, Saudi Arabia

1. Naguib M, Samarkandi AH, Bakhamees HS, Magboul MA, El-Bakry AK. Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine. *British Journal of Anaesthesia* 1995; 75: 588–592.
2. Basta SJ, Savarese JJ, Ali HH, Moss J, Gionfriddo M. Histamine-releasing potencies of atracurium, dimethyl tubocurarine and tubocurarine. *British Journal of Anaesthesia* 1983; 55: 105S–106S.
3. Moss J, Rosow CE, Savarese JJ, Philbin DM, Kniffen KJ. Role of histamine in the hypotensive action of d-tubocurarine in humans. *Anesthesiology* 1981; 55: 19–25.
4. Savarese JJ, Ali HH, Basta SJ, Scott RPF, Embree BP, Wastila WB, Abou-Donia MM, Gelb C. The cardiovascular effects of mivacurium chloride (BW B1090U) in patients receiving nitrous oxide–opiate–barbiturate anesthesia. *Anesthesiology* 1989; 70: 386–394.

Preoperative fasting for paediatric anaesthesia

Sir,—I was surprised to find that reference No. 46 in the article by Phillips, Daborn and Hatch [1] concerning the osmolality of feeding mixtures during experimental injections of milk into tracheas was a reference more than 40 yr old. I would have hoped that the authors would be aware that feeding mixtures, their contents and specifically their osmolality have changed a little during nearly half a century in order to modify those mixtures to resemble human milk as closely as possible. Surely this modification should be considered before one could conclude that formula feeds "cause a greater degree of pulmonary oedema than human or cow's milk when aspirated...".

M. Hopp
Paediatric Endocrine and Growth Clinic
Johannesburg Hospital
University of the Witwatersrand
South Africa

1. Phillips S, Daborn AK, Hatch DJ. Preoperative fasting for paediatric anaesthesia. *British Journal of Anaesthesia* 1994; 73: 529–536.

Sir,—The issue of the relative safety of breast milk and formula feeds remains contentious. It is confused by the variety of types of formula available. Whey based feeds are generally thought to leave the stomach more quickly than feeds with a casein base, but mothers find them less satisfying for their babies. The reference referred to by Dr Hopp was the most recent we could find relating to the pathological changes produced by aspiration of milk. We do not dispute that formula milks have indeed changed but we do not have experimental evidence for what occurs when they are aspirated.

S. Phillips
A. K. Daborn
D. J. Hatch
Royal Sussex County Hospital
Brighton

Use of i.m. temperature probes during cardiopulmonary bypass in humans

Sir,—Benson and colleagues might be forgiven when they write that they could not find reports of i.m. temperature measurements during and after cardiopulmonary bypass (CPB) and that differences between nasopharyngeal and muscle temperatures have not been reported previously [1].

It is probable that recently retired cardiac anaesthetists from the Queen Elizabeth Hospital, Birmingham, would have assured him that i.m. temperature probes have certainly been used for this purpose in the rather distant past. Even my memory, confirmed by my own limited database [2, 3], tells me that such measurements at leg and buttock sites were reported from the Westminster Hospital some years ago and it was common practice in other cardiac units at that time and later. Books published a mere 15 yr ago mentioned placing muscle probes for temperature measurement during cardiac operations [4, 5]. I would expect a more protracted search than my own would reveal many more references to muscle temperature and hypothermic CPB.

Regarding the restoration of muscle temperature to normal body temperature, there is one current view that a degree of hypothermia in the immediate postoperative period after CPB may be advantageous [6] (provided the patient is not allowed to increase muscle tone or shiver). This relates to the fact that subclinical CNS injury is common after CPB [7] and that hypothermia has a protective effect on the brain after any ischaemic event [8]. Striving to restore muscle temperature to normal results in the brain temperature being normal or even above normal towards termination of CPB and this could aggravate any injury [9]. Thus in these days of cost-effectiveness, the trend for rapid rewarming and rapid progress through the cardiac intensive care unit may not be in the best interest of the patient's brain.

J. M. Manners
Chandlers Ford
Hants

1. Benson JP, Patla V, Bonser RS, Hutton P. Use of i.m. temperature probes during cardiopulmonary bypass in humans. *British Journal of Anaesthesia* 1995; 75: 483–485.
2. Cliffe P. The measurement of temperature. *Anaesthesia* 1962; 17: 215–237.
3. Burton GW. Metabolic acidosis during profound hypothermia. *Anaesthesia* 1964; **19**: 365–375.
4. Branthwaite MA. Anaesthesia for open heart surgery. In: Branthwaite MA, ed. *Anaesthesia for Cardiac Surgery and Allied Procedures*. Oxford: Blackwell, 1977; 75–110.
5. Manners JM. Anaesthesia for cardiac surgery. In: Norman J, Whitwam J, eds. *Topical Reviews in Anaesthesia, vol. 1*. Bristol: Wright, 1980; 179–260.
6. Nussmeier NA. Neuropsychiatric complications of cardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia* 1994; **8** (Suppl.): 13–18.
7. Editorial. Cabbages and CABG. *British Medical Journal* 1988; **297**: 1485–1486.
8. Ridenour TR, Warner DS, Todd MM, McAllister AC. Mild hypothermia reduces infarct size resulting from temporary but not permanent focal ischemia in rats. *Stroke* 1992; **23**: 733–738.
9. Drummond JC. Brain protection during anesthesia: a reader's guide. *Anesthesiology* 1993; **79**: 877–879.

Sir,—We are grateful for the opportunity to reply to Dr Manners' letter, some of which we suspect was written rather tongue in cheek. We were unaware of the article by Burton in 1964 and were very interested to read it. Although the other references cited by Dr Manners refer to temperature probes, they in no way invalidate our study or its contribution to the literature. It seems that little, if any, research post-dates that of Burton until the publication of our article and the abstract of Johnson, Desai and Ponte [1]. A repeat detailed search back to 1980 failed to reveal any other relevant research. If any nearly retired anaesthetists have more references, data or unpublished research we would be delighted to hear from them!

With respect to the concept of mild hypothermia and cerebral protection, what evidence there is seems questionable and on the basis of current research the jury is most definitely still out. The prevention of shivering, which is known to jeopardize cerebral oxygenation, is amenable to treatment by conventional, accepted means. It was not our practice to overwarm any patient studied. Our observations which compared deep muscle temperatures with those in the nasopharynx were intended to allow a more rational future therapeutic attack on the problem of afterdrop.

J. P. Benson
P. Hutton
Department of Anaesthesia and Intensive Care
Queen Elizabeth Hospital
Edgbaston, Birmingham

1. Johnson J, Desai J, Ponte J. Observations on muscle temperature changes during cardiopulmonary bypass. *British Journal of Anaesthesia* 1995; 75: 663P.

EEG arousal during laryngoscopy and intubation

Sir,—We read with interest the recent article by Wilder-Smith, Hagon and Tassonyi [1]. The authors observed arousal effects on the EEG after tracheal intubation in patients anaesthetized with either propofol or thiopentone. They stated that the effect site concentrations of both propofol and thiopentone were not in equilibrium, but argued that this was unlikely to have influenced EEG arousal, as it changed abruptly at the time of tracheal intubation. Without control groups, where patients are anaesthetized but the trachea is not intubated, the cause of the arousal cannot be attributed to intubation.

Furthermore, they concluded that propofol depressed nociception more than thiopentone. Without demonstrating the EEG effects with time after boluses of each drug without intubation, it is impossible to draw this conclusion; again a control group is necessary.

C. Shannon
R. McGreggor
M. D. Brunner
Northwick Park and St Mark's NHS Trust
Harrow, Middlesex

1. Wilder-Smith OHG, Hagon O, Tassonyi E. EEG arousal during laryngoscopy and intubation: comparison of thiopentone or propofol supplemented with nitrous oxide. *British Journal of Anaesthesia* 1995; 75: 441–446.

Sir,—We thank Drs Shannon, McGreggor and Brunner for their interest in our study. While we would agree that the concept of a control group not undergoing laryngoscopy and intubation is theoretically attractive, we submit that in practice the absence of such a group does not affect the conclusions drawn from the study. Briefly, these were that the nociception of laryngoscopy and intubation is associated with EEG arousal, and that this arousal is attenuated more by *hypnotically* equipotent doses of propofol than thiopentone, thus suggesting better antinociception by propofol than thiopentone.

The only alternative origin for the EEG "arousal reaction" described is a pharmacological one. While not explicitly stating that the effect site and plasma concentrations of propofol or thiopentone are not in equilibrium, our discussion addressed the issues resulting from that lack of equilibrium, and how unlikely they were to explain the EEG arousal observed. The pharmacological explanation is unsatisfactory for the following reasons:

(1) The EEG is accepted as a good reflection of hypnotic effect site concentrations in the unstimulated subject [1]. In both groups, the EEG time course, and hence the effect site concentration, was similar up to the time of laryngoscopy and intubation. Only in close temporal association with laryngoscopy and intubation does the EEG diverge and change direction abruptly, and this in the context of a previously stable or very slowly changing EEG. This abrupt discontinuity is even clearer in the unprocessed EEG. Such behaviour, distant from the time of injection, is difficult to explain in pharmacokinetic (or pharmacodynamic) terms.

(2) The EEG excitation of the arousal reaction associated with laryngoscopy and intubation is qualitatively and quantitatively different from the EEG excitation known to be of pharmacokinetic origin (i.e. as a result of the presence of excitatory biophase concentrations of anaesthetic agent) and seen earlier in the study. For example, in the thiopentone group, the excitatory EEG arousal reaction with laryngoscopy and intubation was 3–4 times larger and lasted at least three times longer than the earlier EEG excitation of pharmacological origin associated with induction.

(3) The time course of the EEG (and effect site concentrations) during bolus injection of anaesthetic agents in the absence of stimulation such as laryngoscopy and intubation is now well described [1–4] and accessible in the form of modelling programs [5, 6]. An arousal reaction of the type seen in our study, or other types of EEG excitation, did not occur in these models 3–5 min after injection in the absence of stimulation. These models also suggest that effect site concentrations *start* to decrease from their peak 5 min after injection at the earliest, with excitatory effect site concentrations being reached even later.

O. H. G. Wilder-Smith
O. Hagon
E. Tassonyi
Department of Anaesthesiology
Geneva University Hospital
Geneva, Switzerland

1. Bührer M, Maitre PO, Hung OR, Ebling WF, Shafer SL, Stanski DR. Thiopentone pharmacodynamics. I. Defining the pseudo-steady-state serum concentration–EEG effect relationship. *Anesthesiology* 1992; 77: 226–236.
2. Hung OR, Varvel JR, Shafer SL, Stanski DR. Thiopentone pharmacodynamics: II. Quantitation of clinical and electro-

encephalographic depth of anesthesia. *Anesthesiology* 1992; 77: 237–244.
3. Yate PM, Maynard DE, Major E, Frank M, Verniquet AJW, Adams HK, Douglas EJ. Anaesthesia with ICI 35868 monitored by the cerebral function analysing monitor (CFAM). *European Journal of Anaesthesiology* 1986; 3: 159–166.
4. Frank M, Maynard DE, Tsanaclis LM, Major E, Coutinho PE. Changes in cerebral electrical activity measured by the cerebral function analysing monitor following bolus injections of thiopentone. *British Journal of Anaesthesia* 1984; 56: 1075–1081.
5. Shafer SC. *Stanpump*. Available from Steven C. Shafer, Anesthesiology Service (112A), PAVAMC, 3901 Miranda Ave, Palo Alto, CA 94304, USA.
6. Schüttler J, Kloos L. *IVA-SIM*. Available from J. Schüttler, Institut für Anaesthesiologie, Klinikum der Universität Bonn, Bonn, Germany.

Venous thromboembolism and cardiovascular surgery

Sir,—While reading the excellent review article "Prevention of postoperative venous thromboembolism" by Bullingham and Strunin [1], I noticed they stated that patients undergoing bypass or valve surgery are "usually fully anticoagulated" in the "preoperative" period. In the cardiothoracic unit where I am presently working this is not the case. Many patients present having recently taken aspirin (which is normally stopped) and approximately 10 % have received heparin infusions for unstable angina but the majority are not fully anticoagulated. In the peroperative period they are anticoagulated with heparin for bypass and although antagonized with protamine, presumably have a degree of anticoagulation after operation, related mainly to platelet dysfunction. I suggest therefore that the lack of deaths arising from pulmonary embolism in patients undergoing coronary bypass surgery in the NCEPOD study is related to *peroperative* anticoagulation and not to their *preoperative* state.

D. S. McDonald
St George's Hospital
London

1. Bullingham A, Strunin L. Prevention of postoperative venous thromboembolism. *British Journal of Anaesthesia* 1995; 75: 622–630.

Sir,—Dr McDonald has drawn attention to a misprint in our review article [1]. We intended to refer to the effect that *peroperative* and not *preoperative* anticoagulation might have on the incidence of venous thromboembolism after cardiac surgery. As Dr McDonald has pointed out, peroperative anticoagulation is routine for most cardiac operations, while preoperative anticoagulation is uncommon. We thank Dr Mcdonald for drawing our attention to this error.

A. Bullingham
L. Strunin
Anaesthetics Unit
St Bartholomew's and the Royal London Hospital
School of Medicine and Dentistry
The Royal London Hospital
London

1. Bullingham A, Strunin L. Prevention of postoperative venous thromboembolism. *British Journal of Anaesthesia* 1995; 75: 622–630.

Prevention of vomiting after paediatric strabismus surgery

Sir,—While I was very interested in the systematic review of prevention of vomiting after paediatric strabismus surgery [1], I suspect that this methodology has fundamental flaws, particularly if the reviewers are not active practitioners in the field they are reviewing. For example, no mention is made in this analysis of the influence of analgesic technique and tracheal intubation on the occurrence of emesis. As paediatric anaesthetists we know that opioids and tracheal intubation are commonly used for this type of surgery in many countries and that if these two aspects of the technique are avoided where possible, the incidence of postoperative vomiting is very infrequent (< 10 %).

The pain of squint surgery is mostly conjunctival in origin and topical analgesia with drops of amethocaine, oxybuprocaine or NSAID can be used in place of parenteral opioids. It is no longer necessary to intubate the trachea in the majority of children for strabismus surgery with the advent of the laryngeal mask airway.

The conclusion that propofol should not be used in this group is drawn but it is not made clear that this refers to a "propofol infusion for maintenance" technique as opposed to a "propofol for induction, nitrous oxide–oxygen–volatile agent for maintenance" technique.

Therefore, the emetogenic anaesthetic techniques used in the published series which the authors reviewed are in my view obsolete and a move forward to the non-intubation, non-opioid era will have a much greater effect than any antiemetic drug on the prevention of vomiting after paediatric strabismus surgery. Systematic reviews can give a false impression and practising anaesthetists are often "well ahead of the game". In this regard, I think the ethical window for conducting such studies in paediatric strabismus surgery will soon be closed if enough paediatric and children's anaesthetists adopt a more modern approach to these cases.

I strongly commend a propofol–laryngeal mask–topical anaesthesia technique with spontaneous respiration of nitrous oxide–oxygen–volatile agent as day-case anaesthesia for the majority of paediatric squint surgery in terms of its efficacy and lack of emesis. We are currently auditing this assertion but will it be eligible for inclusion in the next systematic review?

N. S. Morton
Department of Paediatric Anaesthesia and Intensive Care
Royal Hospital for Sick Children
Glasgow

1. Tramèr M, Moore A, McQuay H. Prevention of vomiting after paediatric strabismus surgery: a systematic review using the numbers-needed-to-treat method. *British Journal of Anaesthesia* 1995; 75: 556–561.

Sir,—We thank Dr Morton for his interest in our systematic review [1]. However, some of his comments show that we have failed to convey the methodological rules for performing clinical trials and systematic reviews. He advocates his own clinical approach to postoperative vomiting (POV) in paediatric strabismus surgery. We wish to comment on these two issues.

The aim of our study was to compare both efficacy and potential harm of currently used prophylactic antiemetic treatments in a well defined subgroup of patients at particular risk of POV. There were three main results of the combined analysis of all relevant published randomized controlled trials (RCT). First, the mean incidence of POV in controls without antiemetic prophylaxis was more than 50 % (with a wide range). Second, the overall efficacy of prophylaxis compared with placebo or with no treatment or, in the case of propofol, with another anaesthetic technique, was disappointing. Third, the potential of propofol for harm was alarming. As stated in the text and table, propofol as a maintenance regimen was compared with halogenated inhalation anaesthetics.

Evaluating the benefit of any treatment involves making comparisons. The statement that a particular anaesthetic technique decreases the incidence of POV in paediatric strabismus surgery to < 10 % sounds good but is, in the absence of any comparison, no more than a personal view. Before a new therapy is introduced into clinical practice it should have proved to be at least as effective and to induce less harm than old treatments. The widely accepted gold standard to define efficacy and to exclude harm with the least possible bias is the RCT. Clinicians have known for a long time that ignoring this rule may lead to overestimation of treatment effect [2, 3].

All 2044 children in the analysed 27 RCT underwent tracheal intubation. In ophthalmic surgery, as in other situations with more difficult access to the upper airways, many active practitioners, paediatric anaesthetists included, prefer to have the upper airway of the patient secured (i.e. to have the trachea intubated). A laryngeal mask may eventually prove to be less emetogenic than a tracheal tube, but is this technique as safe in paediatric strabismus surgery? Being "well ahead of the game" may have a dark side.

Increasing patient comfort is an attractive target. Decreasing the incidence of POV implies relieving an unpleasant but time limited condition. POV never becomes chronic and almost never kills. Therefore, the level of acceptance of any treatment-induced risk may be low for most clinicians (and patients). Well designed RCT (not audits reflecting personal views) will perhaps show in the near future if the laryngeal mask in paediatric strabismus surgery is advantageous, not only new but also beneficial.

Unfortunately, even paediatric anaesthetists do not know why a particular patient vomits after surgery and another does not. Life would be much easier if we could avoid opioids and tracheal intubation in all children in order to decrease the incidence of POV to less than 10%. One of the most striking results was the extraordinarily wide range of incidences of vomiting in these studies. However, only six studies reported the use of intra-operative opioids [4–9] and in one the incidence of vomiting was very low [7]. Indeed, the highest incidences of vomiting were reported in studies where opioids were avoided [10–12]. While it is widely believed that opioids increase significantly the risk of POV, there is little evidence to support this. The suggested approach with topical analgesia appears original but is not new; recently published experiences from an RCT were not enthusiastic [13].

Clinicians have to balance treatment efficacy and potential for harm. Systematic reviews of relevant RCT with quantitative analysis of extracted data on both efficacy and adverse effects are powerful tools to make this judgement. However, systematic reviews depend on the quality of reports delivering analysable data. Innovative approaches should be subject to trials of appropriate quality. Good practitioners need to understand some methodology, just as systematic reviewers need to have a grasp of clinical realities.

M. Tramèr
A. Moore
H. McQuay
Oxford Pain Relief Unit
Headington, Oxford

1. Tramèr M, Moore A, McQuay H. Prevention of vomiting after paediatric strabismus surgery: a systematic review using the numbers-needed-to-treat method. *British Journal of Anaesthesia* 1995; **75**: 556–561.
2. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. *Journal of the American Medical Association* 1995; **273**: 408–412.
3. Sacks H, Chalmers TC, Smith H. Randomized versus historical controls of clinical trials. *American Journal of Medicine* 1982; **72**: 233–240.
4. Watcha MF, Simeon RM, White PF, Stevens JL. Effect of propofol on the incidence of postoperative vomiting after strabismus surgery in pediatric outpatients. *Anesthesiology* 1991; **75**: 204–209.
5. Snellen FT, Vanacker B, Van Aken H. Propofol–nitrous oxide *versus* thiopental sodium–isoflurane–nitrous oxide for strabismus surgery in children. *Journal of Clinical Anesthesia* 1993; **5**: 37–41.
6. Queinnec MC, de Dieuleveult C, Chupin AM, Pinaud M. Continuous propofol infusion vs enflurane for squint surgery in the child. Comparative study of anaesthetic and recovery conditions. *Annales Françaises d'Anesthésie et de Réanimation* 1989; **8**: 37–41.
7. Pendeville PE, Veyckemans F, Van Boven MJ, Steinier JR. Open placebo controlled comparison of the antiemetic effect of droperidol, metoclopramide or a combination of both in paediatric strabismus surgery. *Acta Anaesthesiologica Belgica* 1993; **44**: 3–10.
8. Rose JB, Martin TM, Corddry DH, Zagnoev M, Kettrick RG. Ondansetron reduces the incidence and severity of poststrabismus vomiting in children. *Anesthesia and Analgesia* 1994; **79**: 486–489.
9. Karlsson E, Larsson LE, Nilsson K. The effects of prophylactic dixyrazine on postoperative vomiting after two different anaesthetic methods for squint surgery in children. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 45–48.
10. Klockgether-Radke A, Feldmann M, Braun U, Muhlendyck H. Antiemetic effects of droperidol versus metoclopramide after strabismus surgery in children. *Anaesthesist* 1992; **41**: 254–259.
11. Lin DM, Furst SR, Rodarte A. A double-blinded comparison of metoclopramide and droperidol for prevention of emesis following strabismus surgery. *Anesthesiology* 1992; **76**: 357–361.
12. Abramowitz MD, Elder PT, Friendly DS, Broughton WL, Epstein BS. Antiemetic effectiveness of intraoperatively administered droperidol in pediatric strabismus surgery—preliminary report of a controlled study. *Journal of Pediatric Ophthalmology and Strabismus* 1981; **18**: 22–27.
13. Heinze J, Ziese P, Ioannakis K. Squint surgery in young children: influence of paracetamol and bupivacaine. *Anaesthesist* 1995; **44**: 312–318.

Maternal sequelae of childbirth

Sir,—Professor Reynolds has drawn attention to the serious neurological complications consequent upon spinal anaesthesia which were described by Ferguson and Watkins in 1938, and by Kennedy, Effron and Perry in 1950 [1–3]. Professor Reynolds attributes these complications solely to the neurotoxicity of the spinal anaesthetic solutions used, which is a satisfactory explanation for most of the cases in Ferguson and Watkins' case series. However, medical opinion has held that the more persistent and serious neurological disabilities such as were described by Kennedy's team could not all be ascribed to local anaesthetic neurotoxicity and that the problem has yet to be understood fully [4].

The Woolley and Roe case [4] has since demonstrated that spinal anaesthetic solutions can be contaminated with acid from spinal needles and syringes if descaling solutions are not washed out of water boiler sterilizers. As these water boilers would have been used when Kennedy's patients were given their spinal anaesthetics, acid contamination is a plausible explanation for these tragedies also. Confirmation at laminectomy of adhesive arachnoiditis (one of the consequences of damage by acid) in four of Kennedy's patients supports this explanation.

These water boilers remain in use today in parts of the world where medical facilities are less well developed, and the potential risk which they pose would not have become clear without this re-evaluation of an apparently unrelated historical problem. Yet again we see that an awareness of history protects us from repeating earlier mistakes.

C. D. D. Hutter
City Hospital
Nottingham

1. Reynolds F. Maternal sequelae of childbirth. *British Journal of Anaesthesia* 1995; **75**: 515–516.
2. Ferguson FR, Watkins KH. Paralysis of the bladder and associated neurological sequelae of spinal anaesthesia (cauda equina syndrome). *British Journal of Surgery* 1938; **25**: 735–752.
3. Kennedy F, Effron AS, Perry G. The grave spinal cord paralyses caused by spinal anesthesia. *Surgery, Gynecology and Obstetrics* 1950; **91**: 385–398.
4. Hutter CDD. The Woolley and Roe case. A reassessment. *Anaesthesia* 1990; **45**: 859–864.

Sir,—I thank Dr Hutter for his interest in my editorial. I did not, however, intend to leave readers with the impression that I attributed neurological sequelae of spinal anaesthesia in the 1930s and 1950s to local anaesthetic neurotoxicity. What I actually referred to were neurotoxic *formulations* and *techniques*. Readers might be interested to hear that the formulation of procaine that was used for spinal anaesthesia in 14 cases of cauda equina syndrome reported from Manchester contained 10% procaine, glycerine and either gliadin or gum acacia, in 15% alcohol [1]. The idea of this formulation, termed heavy duracaine, was to prolong the action of procaine, an odd choice since cinchocaine, a very long-acting drug, was available then. The *technique* I referred to was the light spinal technique which involved displacement of a large volume of cerebrospinal fluid by a foreign solution. I acknowledge that this solution itself may have been contaminated, although like Dr Hutter I would not subscribe to the phenol-entering-invisible-cracks theory. However, it was not, as Dr Hutter suggests, the Woolley and Roe cases that demonstrated that spinal injections may have been contaminated with acid from sterilizers, but Dr Hutter himself [2]. His article gives a fascinating account of his investigation of these cases and the development of his hypothesis.

The western world may congratulate itself on having left behind the amazing concoctions of the 1930s, the light spinal technique using 10 ml of hypobaric cinchocaine, boiling water sterilizers, soaking ampoules in phenol, etc. Nevertheless, recent accounts of neurotoxicity after accidental total spinal anaesthesia [3, 4] and puddling in the subarachnoid space of apparently respectable 2–5 % lignocaine solutions [5–7] must remind us how easily injections into the subarachnoid space may cause radicular irritation and even cauda equina syndrome. Perhaps we have reason to be thankful that in the UK bupivacaine rather than lignocaine is used for spinal anaesthesia.

F. Reynolds
St Thomas's Hospital
London

1. Ferguson FR, Watkins KH. Paralysis of the bladder and associated neurological sequelae of spinal anaesthesia (cauda equina syndrome). *British Journal of Surgery* 1938; **25**: 735–752.
2. Hutter CDD. The Woolley and Roe case. A reassessment. *Anaesthesia* 1990; **45**: 859–864.
3. Drasner K, Rigler M, Sessler D, Stoller M. Cauda equina syndrome following intended epidural anesthesia. *Anesthesiology* 1992; **77**: 582–585.
4. Cheng A. Intended epidural anesthesia as possible cause of cauda equina syndrome. *Anesthesia and Analgesia* 1993; **78**: 157–159.
5. Fenerty J, Sonner J, Sakura S, Drasner K. Transient radicular pain following spinal anesthesia. Review of the literature and report of a case involving 2 % lignocaine. *International Journal of Obstetric Anesthesia* 1996; **5**: 32–35.
6. Snyder R, Hui G, Flugstad P, Viarengo C. More cases of possible neurologic toxicity associated with single subarachnoid injections of 5 % hyperbaric lidocaine. *Anesthesia and Analgesia* 1994; **78**: 411.
7. Rigler M, Drasner K, Krejcie T. Cauda equina syndrome after continuous spinal anesthesia. *Anesthesia and Analgesia* 1991; **72**: 275–281.

Venous air embolism: is end-tidal oxygen monitoring more informative than end-tidal carbon dioxide?

Sir,—We read with interest the article by Kyttä and colleagues [1] on monitoring lung compliance and end-tidal oxygen content for the detection of venous air embolism and wish to make some comments.

The authors used 100 % oxygen with 0.5–0.7 % isoflurane for maintenance of anaesthesia during posterior fossa surgery. The use of less than 1 MAC of isoflurane in oxygen during maintenance of anaesthesia is likely to be associated with awareness. Although many neuroanaesthetists have abandoned nitrous oxide during intracranial surgery, it is still being used in various centres worldwide and would have decreased the likelihood of awareness. We presume that the authors considered that the use of nitrous oxide would increase the incidence of air embolism, but it has been demonstrated that this is not the case in neurosurgical patients undergoing surgery in the sitting position [2]. Alternatively, a mixture of oxygen in air with an FI_{O_2} of 0.3–0.4 and a concentration of isoflurane in excess of 1 MAC or an infusion of i.v. anaesthetic agents can be used for maintenance of anaesthesia during neurosurgical operations.

PEEP was used for the prevention of air embolism in the sitting position, despite the associated reduction in venous return and cardiovascular instability. As a result of an increase in right atrial pressure, PEEP should reduce the pressure gradient between the cerebral venous sinuses and the right atrium. However, it has been demonstrated that PEEP has little value in the prevention of venous air embolism [3]. Moreover, the authors used hyperventilation with PEEP in their anaesthetic technique. Hyperventilation has been shown to reduce the transverse sinus pressure to within the atmospheric to subatmospheric range which could increase the risk of air embolism. Moderate hypoventilation has been recommended during the most critical period of exposing the posterior fossa followed by normoventilation when surgery of the lesion has begun [4].

In this study, the decrease in the difference between inspired and end-tidal oxygen content was 2–2.5 % during induced air embolism in animals breathing 100 % oxygen. This may be consequent on alteration in composition of alveolar gases as a result of a sudden reduction in end-tidal carbon dioxide concentration. This decrease in the difference in inspired and end-tidal oxygen concentration may not be as great when maintaining anaesthesia with oxygen–air or oxygen–nitrous oxide with an FI_{O_2} of 0.3–0.4. As air embolism is being reported increasingly after operations other than neurosurgery, the results would have been more applicable to clinical practice if an inspired oxygen concentration of 30–40 % had been used. In this study, the increase in end-tidal oxygen content occurred after the changes in end-tidal carbon dioxide concentration. In clinical practice, when air embolism is suspected because of a reduction in end-tidal carbon dioxide concentration, the oxygen in the inspired mixture is increased immediately to 100 %. Therefore, at that time the end-tidal and inspired oxygen content difference may not be of value in monitoring for detection of air embolism.

The increase in peak airway pressure reflects a decrease in dynamic pulmonary compliance if tidal volume is constant. The authors recorded an average increase in peak airway pressure of less than 1 cm H_2O subsequent to induced air embolism in animals. This is a small increase and it is doubtful if it would be sufficiently reliable to be a useful monitor in clinical practice. Changes in airway pressure of this magnitude are not uncommon during uneventful anaesthesia and surgery. The results of this study confirm that dynamic pulmonary compliance is a less sensitive monitor than end-tidal carbon dioxide concentration in the early detection of air embolism. It has been demonstrated previously that the increase in airway pressure should not be relied upon as a monitoring aid for detection of venous air embolism [5]. The large variability of the change in airway pressure (SEM 2.0–3.0 cm H_2O) in the animal study supports this argument.

A. Mallick
E. Moss
Academic Unit of Anaesthesia
The General Infirmary at Leeds
Leeds

1. Kyttä J, Randell T, Tanskanen P, Kajimoto Y, Rosenberg PH. Monitoring lung compliance and end-tidal oxygen content for the detection of venous air embolism. *British Journal of Anaesthesia* 1995; **75**: 447–451.
2. Losasso TJ, Muzzi DA, Dietz NM, Cucchiara RF. Fifty percent nitrous oxide does not increase the risk of venous air embolism in neurosurgical patients operated upon in the sitting position. *Anesthesiology* 1992; **77**: 21–30.
3. Lubnin A, Oskanova M. Prevention of air embolism in neurosurgical patients operated on in a sitting posture: a comparative study of 3 methods. *Anesteziologiia i Reanimatologiia* 1994; **5**: 22–26.
4. Zentner J, Albrecht T, Hassler W. Prevention of an air embolism by moderate hypoventilation during surgery in sitting position. *Neurosurgery* 1991; **28**: 705–708.
5. Dash HH, Bithal PK, Joshi S, Saini SS. Airway pressure monitoring as an aid in the diagnosis of air embolism. *Journal of Neurosurgical Anesthesiology* 1993; **5**: 159–163.

Sir,—Thank you for the opportunity to reply to the correspondence on our recent study on the detection of venous air embolism [1].

Our standard regimen in maintaining anaesthesia during posterior fossa surgery includes high-dose fentanyl and pancuronium as needed, in addition to an end-tidal concentration of 0.5–0.7 % of isoflurane in oxygen. Awareness has not been reported by any of our patients. Higher concentrations of isoflurane may cause haemodynamic lability in patients undergoing surgery in the sitting position.

The use of nitrous oxide in neuroanaesthesia is controversial. In patients at risk of venous air embolism (VAE) it is not recommended as it may increase the size of the air bubbles resulting in more pronounced consequences of air embolism [2]. The incidence of VAE cannot be expected to decrease on abandoning nitrous oxide, the occurrence of VAE being dependent mainly on the surgical technique and positioning of the patient.

There is no evidence of possible detrimental effects of low PEEP in neurosurgical patients. In our experimental study, no PEEP was applied. In the study of Zentner, Albrecht and Hassler [3], hypoventilation was recommended for the prevention of VAE during posterior fossa surgery. However, in the editorial comment by Roy F. Cucchiara, it was pointed out that hypoventilation compromises surgical exposure. We agree with the latter, and do not hypoventilate the lungs of our patients.

Changes in the differences between inspired and expired oxygen content were significant in this particular experimental setting. We agree with the correspondent that the changes do not follow a similar pattern if oxygen in air or oxygen in nitrous oxide are used as inspiratory gases during maintenance of anaesthesia [Kyttä, Randell, Tanskanen, unpublished observation, manuscript in preparation].

We did not recommend the use of changes in peak airway pressure for the detection of VAE. However, the decreases observed in dynamic lung compliance were more pronounced and followed VAE consistently. For calculation of dynamic lung compliance, changes in airway pressures during the respiratory cycle and changes in tidal volume are used. We still hold to our conclusion that monitoring of inspiratory to expiratory oxygen concentration, and dynamic lung compliance are valuable *supplements to other monitoring techniques* for the detection of pulmonary VAE [1].

J. KYTTÄ
T. RANDELL
P. TANSKANEN
Department of Anaesthesiology
Töölö Hospital
Helsinki, Finland

1. Kyttä J, Randell T, Tanskanen P, Kajimoto Y, Rosenberg PH. Monitoring lung compliance and end-tidal oxygen content for the detection of venous air embolism. *British Journal of Anaesthesia* 1995; 75: 447–451.
2. Lam AM, Mayberg TS. Use of nitrous oxide in neuroanesthesia: Why bother? *Journal of Neurosurgical Anesthesiology* 1992; 4: 285–289.
3. Zentner J, Albrecht T, Hassler W. Prevention of an air embolism by moderate hypoventilation during surgery in the sitting position. *Neurosurgery* 1991; 28: 705–708.

Spinal anaesthesia for Caesarean section in women with incomplete extradural analgesia

Sir,—The requirement for operative delivery in the event of inadequate extradural block is not an uncommon problem in obstetric anaesthesia, requiring an alternative anaesthetic technique. Spinal anaesthesia would appear to offer many benefits in this situation and has been recommended [1]. However, six recent case reports describing unacceptably high spinal block in 10 parturients have called into question the safety of spinal anaesthesia where there is existing extradural block [2–7].

Several theories have been proposed to account for these unexpected high block levels including: compression of the dural sac by fluid in the extradural space [8]; leakage of extradural local anaesthetic through the dural hole [9]; the existence of subclinical analgesia at a higher spinal level [10]; or continuing spread of the spinal independent of the extradural.

However, in these cited case reports, seven of the 10 women had the spinal inserted in the sitting position, while nine of 10 were placed in the wedged supine position after spinal anaesthesia. It is our contention that the key to the eventual height of the spinal block in such circumstances is the position of the patient during and after insertion of the spinal and that spinal anaesthesia may be used safely in the presence of extradural block provided there is meticulous attention to patient positioning.

To study this, we have performed spinal anaesthesia in 12 women (mean age 29 yr, mean weight 80 (SD 13) kg, mean height 163 (6) cm) presenting for emergency Caesarean section who had inadequate extradural block for a variety of reasons such as: unblocked segment; unilateral block; maternal dissatisfaction with the extradural; or because we considered that the urgency of the situation did not allow time for the extradural to be extended.

Six of the women had received extradural infusions and six bolus doses of bupivacaine extradurally. Block height before spinal anaesthesia varied from L2 to T8 (median T12). Doses of drugs given extradurally before spinal anaesthesia was commenced varied considerably. The median dose of bupivacaine was 102 (range 25–225) mg, the median dose of fentanyl 10 (0–200) µg. A crystalloid preload of 1000 ml was given and the extradural catheter removed. The patient was positioned in the left lateral position with two pillows under the head and shoulders such that the spine was maintained with the cervical spine higher than the lumbar spine. Spinal anaesthesia was produced using 0.5% hyperbaric bupivacaine 2.5 ml with fentanyl 10 µg via a 25-gauge Whitacre needle. The patient was then turned immediately to the right lateral position, maintaining the position of the spine as before.

Block height was assessed 5 min after spinal injection and every 5 min thereafter. Reverse Trendelenburg tilt was used to prevent the block spreading in a cephalad direction and Trendelenburg tilt used where necessary to develop the height of the block, aiming at a final block height of T4. After 20 min, the patient was turned to the supine position with a left lumbar wedge and prepared for surgery. Median final block height was T3 (range T3–6). Median systolic pressure was 96 (range 85–126) mm Hg, maintained with i.v. ephedrine where necessary (maximum dose 15 mg).

While we have not attempted to define the cause(s) of the reported high blocks, we have shown in this small series that unacceptably high spinal block may be prevented by careful positioning during and after subarachnoid injection.

M. STONEHAM
Stoke Mandeville Hospital
Aylesbury
A. SOUTER
John Radcliffe Hospital
Oxford

1. Kestin IG. Spinal anaesthesia in obstetrics. *British Journal of Anaesthesia* 1991; 66: 596–607.
2. Stone PA, Thorburn J, Lamb KSR. Complications of spinal anaesthesia following extradural block for Caesarean section. *British Journal of Anaesthesia* 1989; 62: 335–337.
3. Beck GN, Griffiths AG. Failed extradural anaesthesia for Caesarean section. Complication of subsequent spinal block. *Anaesthesia* 1992; 47: 690–692.
4. Mets B, Broccoli E, Brown AR. Is spinal anesthesia after failed extradural anesthesia contraindicated for Cesarean section? *Anesthesia and Analgesia* 1993; 77: 629–631.
5. Dell RG, Orlikowski CEP. Unexpectedly high spinal anaesthesia following failed extradural anaesthesia for Caesarean section. *Anaesthesia* 1993; 48: 641.
6. Gupta A, Enlund G, Bengtsson M, Sjöberg F. Spinal anesthesia for Cesarean section following epidural analgesia in labor: a relative contraindication. *International Journal of Obstetric Anesthesia* 1994; 3: 153–156.
7. Furst SR, Reisner LS. Risk of high spinal anesthesia following failed epidural block for cesarean delivery. *Journal of Clinical Anesthesia* 1995; 7: 71–74.
8. Blumgart CH, Ryall D, Dennison B, Thompson-Hill LM. Mechanism of extension of spinal anaesthesia by extradural injection of local anaesthetic. *British Journal of Anaesthesia* 1992; 69: 457–460.
9. Bernards CM, Kopacz DJ, Michel MZ. Effect of needle puncture on morphine and lidocaine flux through the spinal meninges of the monkey in vitro. *Anesthesiology* 1994; 80: 853–858.
10. Carrie LES. Epidural versus combined spinal epidural block for Caesarean section. *Acta Anaesthesiological Scandinavica* 1988; 32: 595–596.

British Journal of Anaesthesia 1996; 76: 477

BOOK REVIEWS

Primer of Intraoperative Neurophysiologic Monitoring. G. B. Russell and L. D. Rodichock (editors). Published by Butterworth-Heinemann, Oxford. Pp. 331; indexed; illustrated. Price £50.00.

This book of 331 pages comprises 25 referenced chapters written by 26 contributing authors from Pennsylvania, Utah, North Carolina and Canada. The book can be divided broadly into two sections; the larger first section covers electrical monitoring, the first two chapters being devoted to the history and functional neuroanatomy, and the next 17 chapters cover various aspects of EEG and evoked potential monitoring. The subsequent smaller section comprises a series of chapters dealing with intraoperative monitoring using intracranial pressure, transcranial Doppler and cerebral oximetry.

Although this book is packed with useful information on neurophysiological monitoring, I found it difficult to read, because chapters vary in their style of writing and there is considerable repetition. Some of the chapters contain largely technical information on EEG or evoked potential monitoring, while others are styled more towards the practical use of these techniques and the problems encountered during anaesthesia for neurosurgical procedures.

Overall this book would be easier to read had the editors streamlined it into a smaller number of more comprehensive chapters. Nevertheless, some chapters are sufficiently comprehensive to be useful reading in their own right for the anaesthetist. For example, chapter 5 gives a broad review of the components of an EEG machine, different methods of monitoring EEG and the particular problems encountered in the operating theatre environment. Chapter 12 gives a detailed analysis of evoked potentials with reference to the effects of anaesthetic agents and is particularly valuable as it discusses in detail the interpretation of evoked potentials during operations, as illustrated by case reports. Chapter 18 is of particular interest to the anaesthetist as it covers the pharmacological effects of anaesthesia on neurophysiological monitoring. Chapter 20 gives an interesting insight into the assessment and response that is appropriate to anomalies detected during intraoperative electrophysiological monitoring and discusses in detail the relative sensitivity and specificity of the monitoring techniques for different operative procedures.

The later chapters of the book are written in a different style and provide an overview of monitoring techniques that might be of value in the future in the operating theatre environment, but the chapters are well referenced and would be a good starting source for those interested in these subjects.

In summary, although this book contains excellent information it is rather disjointed with much repetition. I believe editing the book into a smaller number of more comprehensive chapters would have greatly assisted the reader in identifying specific areas of interest when using this book as a reference. Nevertheless, there are several chapters which would be of interest to an anaesthetist involved in neurophysiological intraoperative monitoring.

N. M. Dearden

Wylie & Churchill-Davidson's A Practice of Anaesthesia, 6th Edn. T. E. J. Healy and P. J. Cohen (editors). Published by Edward Arnold, London. Pp. 1536; indexed; illustrated.

Wylie and Churchill-Davidson's A Practice of Anaesthesia was first published in 1960 and soon became established as a standard text. Regular updates culminated in the production of the fifth edition in 1984. However, there were no further editions; that is until now, 11 years later. Consequently, this edition represents a major rewrite orchestrated by the two editors, Thomas Healy and Peter Cohen. They have been successful in producing a fine textbook which contains considerably more chapters compared with previous editions. They have managed also to keep the contents in one large volume and endeavoured to cover all aspects of modern day international anaesthetic practice.

The book comprises 26 chapters, many by well known experts from Europe, USA and Australasia, and is well indexed. In general, the references are useful and recent, with many helpful suggestions for further reading.

The book is set out in four sections. The first section covers history and basic science. Each chapter provides a good summary of the basic principles on which anaesthetic practice is based. Generally, these chapters are well written and supported by many excellent diagrams and tables. Apart from the standard choice of subject matter, several relatively new and topical subjects have been included, for example autologous blood transfusion, computers in anaesthesia, calcium and magnesium in anaesthesia and transmission of infection in the operating theatre. Space has not allowed several of these chapters to be comprehensive and detailed; consequently, some subjects are covered briefly. However, a full treatment of basic principles and science is not the purpose of this book and the chapters provide a useful reminder before moving on to the next section.

Section 2 sets out to describe the principles of clinical practice in general areas such as paediatrics, geriatrics, hepatic failure, renal failure, recovery, nutritional support and postoperative analgesia. Apart from these and other standard topics, particularly good and interesting accounts of patient safety, critical incidents, the difficult airway, hyperbaric medicine, trauma associated with patient transfer and positioning are available.

The third section confines itself to a systematic treatment of anaesthetic practice, as applied to specific specialties. Many of these chapters are particularly good and often supported by excellent photographs. However, probably because of size constraints, a few areas are dealt with rather briefly. Despite the intent to appeal on both sides of the Atlantic, the European reader is not aware of any potential conflict in approach.

The final section of the book is imaginative and covers topics not often discussed in large textbooks, for example medicolegal matters, quality assurance, cost management and ethical considerations. The authors have supplied good accounts of these difficult areas; it is particularly interesting to compare the chapter describing legal matters in the UK with that discussing the situation in the USA.

I found this textbook a delight to read. It would be useful to any practising anaesthetist, particularly those studying for the final FRCA examination. The decision to confine the subject matter to one volume has led inevitably to brevity in some areas but the editors are to be congratulated in producing an excellent new textbook following the distinguished tradition of Wylie and Churchill-Davidson.

D. Rowbotham

Papers for publication and all editorial communications should be addressed to:
Professor G. Smith,
Editor, British Journal of Anaesthesia,
University Department of Anaesthesia,
Leicester Royal Infirmary,
Leicester LE1 5WW.
Telephone: 0116 247 0141
Fax: 0116 285 4487

All **business communications** should be sent to the Publishers: Professional & Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR.

The GUIDE TO CONTRIBUTORS may be found in the advertisement section of any issue of the journal (pages ii, iv & vi).
Published monthly. Annual subscriptions: Worldwide £156.00; USA only $245.00 (direct orders only). Trainee rate: Worldwide £75.00. Airmail rates on application. ISSN 0007–0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR. Orders in the USA may be sent to Professional and Scientific Publications, PO Box 408, Franklin, MA 02038, USA.

"WIREX" self-binding cases, which hold a complete volume, i.e. 6 months with room for a supplement and annual handbook, are now available. Price UK £14.00 per two binders, Europe £20.00 per two binders (to cover 1 year). Price includes postage and packing. Rest of the World prices on application. Cheque with order to Hethersett Supplies, Mount Bovers Lane, Hawkwell, Essex SS5 4JA, Tel. (01702) 202393.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statements appear in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statements. Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

© Copyright: 1996 *British Journal of Anaesthesia*
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia*, requests for which should be addressed to the **Publishers**.

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge.

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 76, No. 4 APRIL 1996

EDITORIAL I

The 11th World Congress of Anaesthesiology

This issue of the journal marks the occasion of the 11th World Congress of Anaesthesiology which is being held in Sydney, Australia. The over-printing on the front cover of this issue does not signify a special issue or a particularly special selection of manuscripts for publication; it is intended to commemorate the occasion of the World Congress and signifies that *British Journal of Anaesthesia*, being a truly international journal of anaesthesia, will be represented during the congress, both by an exhibition stand staffed by our publishers and also active participation by several members of the Editorial Board in a session on anaesthesia publications.

The international nature of *British Journal of Anaesthesia* is exemplified by our readership, with more than 50% of our subscribers based outside the UK, and by the origin of the material published in each issue of the journal. In this present unselected issue, we have articles from Australia, Denmark, France, Japan, New Zealand, Switzerland and the USA, with only 50% of manuscripts originating from within the UK. In many issues of the journal, articles from outside the UK greatly exceed the number of those from the UK. The gradual policy which the Board of the *BJA* has pursued in making the journal more international is also reflected in the fact that since the last World Congress of Anaesthesiology, held in the Hague in 1992, new members of the Board of the journal have been recruited from the USA, Germany and Australia, and the Board is still actively seeking additional members from outside the UK. It is also perhaps appropriate in this World Congress issue to describe two major innovations in publishing technology for the journal for 1996; namely, printing from disk and publication of a CD-ROM.

Before this year, the process of publishing the journal involved submission of hard copy from authors to the editor, and onward transmission of edited manuscripts to a technical editor who made technical adjustments and marked up the copy for specialist typesetters situated at our printers, Cambridge University Press. The typesetters had the role of keying manuscripts onto computer from hard copy. However, in 1996, this process of typesetting will be eliminated and it will be possible for manuscripts to be handled in disk form, with editing of disks on screen by our technical subeditor and printing directly from that disk, thereby eliminating the tier of typesetters in the printing process. The origination of the pages will be performed at our publishers and at the same time an SGML (standard generalized mark-up language)-encoded neutral form of each article will be locked away in a database. This will enable any material in *BJA* to be re-used for online publishing, collected article publications and perhaps in other technologies which will be developed in future. DTP (desk-top publishing) has been used for many years in other branches of the publishing industry but it is being introduced more slowly in such conservative organizations as monthly scientific journals. For the reader, this should have benefits in reducing the number of potential printing errors, and for authors, it should enable us to reduce the period between acceptance of a manuscript and subsequent publication. Currently, the *BJA* has a good acceptance to publication interval which averaged 4½ months for the period December 1995 to March 1996; our technological innovation should enable us to achieve a potential reduction of 20 days in this process. There will be other additional benefits which will not be as obvious to the reader, such as automated computerized indexing and facilities for electronic transmission of the journal.

The second major exciting technological innovation with which the journal is associated in 1996 is the production of a CD-ROM which has been termed TEAL (the electronic anaesthesiology library). Not only does this represent a major advance in anaesthesia publishing technology but it also allows an exciting collaboration between four major international journals: *Anesthesiology*, *Anesthesia and Analgesia*, *British Journal of Anaesthesia* and *Canadian Journal of Anaesthesia*. In the past year, these four journals have been collaborating in this venture and agreement was reached in producing a single CD-ROM which will incorporate 5 yr of contents (1991–1995) inclusive of all issues of these journals. All of the contents will be featured, including review articles, but abstracts of proceedings of scientific meetings and symposia that are not regular issues will be excluded. In addition, Medline abstracts to all cited references in the four journals within this 5-yr period will also be included on the same disk. This will enable the reader, during perusal of a manuscript, to access instantly on screen an abstract of any article published in this era in any other biomedical journal incorporated on Medline.

The first demonstration of TEAL took place at the 1995 American Society of Anesthesiology Meeting. The demonstration CD contained the contents of the two US journals for 2 yr. At the World Congress in Sydney, there will be a demonstration of a disk containing 3 yr of contents of all four journals. The scheduled publication date for the final version of TEAL is July 1996 and it is now possible to place advance orders. The disk will contain the full 5-yr contents from all four journals with the Medline abstracts on a single CD-ROM. The Boards of the four journals have agreed that, in future, TEAL will be produced in a 5-yr rolling updated format, that is the annual update disk will contain a rolling 5-yr disk set, 1992–1996, 1993–1997, 1994–1998 and so on. It is important to note that the copyright of material on TEAL will remain vested in each of the four respective journals.

The proposed search engine for TEAL will be based on fuzzy logic. This will enable material to be brought up within seconds of typing in a search word. The fuzzy logic component also allows considerable latitude in accuracy of the search word, that is it will respond to either US or British spelling, or even misspelling!

TEAL will allow extremely rapid access to articles with appearance of material on screen as in the printed page of the original journal. It will be possible to print out in the same format as the articles appeared in the printed journal. Other extremely useful features include the ability to reproduce images in as good or better quality than the original printed version and also magnification of some images. It is notable that the cost of TEAL will be considerably cheaper than the cost of binding the journals described on the disk.

TEAL will be demonstrated in the exhibition area at the World Congress and we hope that delegates will take the opportunity to assess the power of this innovation. The editors of the four journals involved in TEAL were extremely enthusiastic and unanimous in their support for the project which has been brought to fruition in an amazingly short time since this concept was first discussed—a superb example of international co-operation. We hope that our enthusiasm is shared by our subscribers and that TEAL proves to be of great value to all anaesthetists, enabling more rapid access to the important and recent international anaesthetic literature.

G. SMITH
Editor

British Journal of Anaesthesia 1996; **76**: 481–483

EDITORIAL II

Rocuronium: the newest aminosteroid neuromuscular blocking drug

Yet another non-depolarizing neuromuscular blocking drug may seem, especially to the older generation of anaesthetists, unnecessary. This is not so. We require a non-depolarizing agent with a rapid onset of action, in common with suxamethonium, but with a clinical duration of 10–12 min. Such an agent would not have the side effects associated with depolarizing drugs (e.g. hyperkalaemia, increased intraocular pressure, muscle pains) and ideally, its disposal would be independent of organ function.

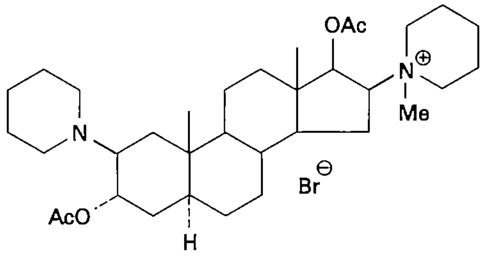
It has perhaps been forgotten that when atracurium and vecuronium became available in 1982, both agents were found to have a shorter onset of action than the pre-existing non-depolarizing drugs. Maximum block after atracurium 0.5 mg kg^{-1} was achieved within 2.0 min, and after vecuronium 0.1 mg kg^{-1}, within 3 min [1]. These onset times were shorter than after tubocurarine 0.6 mg kg^{-1} at nearly 4.0 min [1], but were still longer than after suxamethonium 1.0 mg kg^{-1}. The depolarizing agent could be relied upon to produce maximum block within 1 min and, of the utmost importance, there was little variation in effect between individuals: the SD of that response was only 12 s [2].

In 1994, a new drug became available which narrowed this gap between the onset of action of suxamethonium and the non-depolarizing neuromuscular blocking drugs. Rocuronium has a similar structure to those of pancuronium and vecuronium (fig. 1). In common with vecuronium, rocuronium is a monoquaternary aminosteroid, but it is much less potent, with an ED_{95} (the dose required to produce 95% depression of the twitch response) of 0.3 mg kg^{-1} [3]. This lack of potency is thought to be an important factor in determining onset of neuromuscular block [4]. Whichever neuromuscular blocking drug is used, nearly all of the molecules at the neuromuscular junction are bound to the postsynaptic nicotinic receptor. The majority of these receptors must be occupied to produce neuromuscular block [5]; thus the number of molecules of a neuromuscular blocking drug which must enter the neuromuscular junction to produce a given degree of block is constant. But within a series of compounds, a less potent drug is given in a higher dose; a larger number of molecules are available to diffuse into the neuromuscular junction than the smaller number of molecules of a potent drug. A rapid onset of action is more likely to be achieved with a less potent agent.

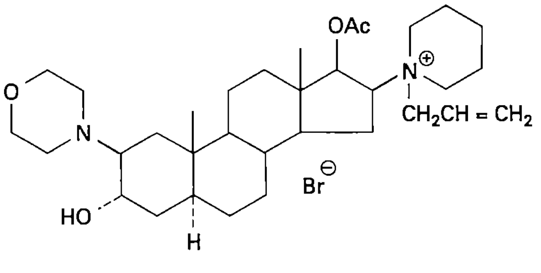
Onset of block

Vecuronium has an ED_{95} of 0.056 mg kg^{-1} [6] and pancuronium an ED_{95} of 0.064 mg kg^{-1} [6]. It would therefore be expected that rocuronium, with an ED_{95} of 0.3 mg kg^{-1}, should have a more rapid onset of action than the older aminosteroids. Early clinical reports confirmed this. Rocuronium 0.6 mg kg^{-1} ($2 \times ED_{95}$) was found to have an onset of action of 60–90 s at the adductor pollicis muscle [7, 8]. The rate of onset is affected by anaesthetic technique: if the neuromuscular blocker is given immediately after the induction agent, then the onset time is a few seconds longer than in a research study, when steady-state anaesthesia has already been achieved with a volatile agent. At this dose, the block produced by rocuronium was not quite as predictable as suxamethonium: the range of effect was greater [9]. If the dose is doubled to 1.2 mg kg^{-1}, intubating conditions very similar to those produced by suxamethonium 1.0 mg kg^{-1} can be achieved reliably [9], but this dose of rocuronium ($4 \times ED_{95}$) has a duration comparable with that of pancuronium 0.1 mg kg^{-1}. Even with a small dose of rocuronium (0.45 mg kg^{-1}), a mean time to maximum effect of 72 s during halothane anaesthesia has been reported, although with an SD of almost 20 s [10].

As with other non-depolarizing neuromuscular blocking drugs, the laryngeal adductor muscles are more resistant to rocuronium than the adductor pollicis muscle (where neuromuscular block is often mentioned). After rocuronium 0.8 mg kg^{-1}, the peak effect in the laryngeal muscles is later, more variable and less profound than after suxamethonium 1.0 mg kg^{-1} [11]. The diaphragm is also more resistant to rocuronium than the adductor pollicis: an intubating dose of rocuronium 0.6 mg kg^{-1} has an effect at the diaphragm comparable with 0.5 mg kg^{-1} in the adductor pollicis [12]. Complete neuromuscu-



Vecuronium



Rocuronium

Figure 1 The monoquaternary aminosteroid, vecuronium, has an acetyl (AcO) group at the 3-carbon position. Deacetylation of vecuronium in the liver produces a 3-hydroxy metabolite which has approximately 50% of the neuromuscular blocking potency of vecuronium [23]. Rocuronium has a hydroxyl group at the 3-carbon position; unlike vecuronium, it will not undergo de-acetylation to produce a 3-OH metabolite with neuromuscular blocking activity.

lar block of the adductor pollicis does not imply that the laryngeal muscles and diaphragm are also completely paralysed.

If it is desirable to achieve a rapid onset of neuromuscular block and suxamethonium is contraindicated, for example in an emergency procedure in a patient with hyperkalaemia, or a patient with a penetrating eye injury, then rocuronium, in a dose of at least $2 \times ED_{95}$ (0.6 mg kg^{-1}), has a distinct advantage over other non-depolarizing neuromuscular blocking drugs. It is also preferable to a small "priming" dose of any other non-depolarizing neuromuscular blocking drug, before a paralysing dose, in an attempt to shorten the time to onset of maximum block [13]; there is no risk of curarization in a conscious patient.

If difficult intubation is anticipated, speed of onset of action is not of the utmost importance: profound block is required, from which rapid recovery can be obtained, if all attempts at intubation fail. In such cases, suxamethonium is still the ideal agent to use, because rocuronium is not a short-acting drug.

Recovery from block

Ten percent recovery of the first twitch of the train-of-four response (T1/T0) after rocuronium 0.45 mg kg^{-1} occurs in a mean time of 27 min during halothane anaesthesia [10]. During isoflurane anaesthesia, 10% recovery of T1/T0 after rocuronium 0.6 mg kg^{-1} occurs in 34 min and 25% recovery in 42 min [14]. After vecuronium 0.1 mg kg^{-1} in patients receiving neuroleptanaesthesia, 10% recovery also occurs in a mean time of 27 min [1], and 25% recovery in 44 min [15]. As with other aminosteroid neuromuscular blocking drugs, potentiation of rocuronium is greater during enflurane or isoflurane anaesthesia than during neuroleptanaesthesia [16], and neostigmine is more effective than edrophonium in antagonizing fade of the train-of-four response at the end of surgery [17].

Thus rocuronium does not have a short duration of action. Moreover, recovery from neuromuscular block occurs during drug redistribution, but the elimination half-life of rocuronium of 86 min [10] is longer than that for vecuronium (53 min) [18].

Renal failure patients

Animal studies have suggested that rocuronium is metabolized in the liver and excreted in bile; in cats, less than 10% of a bolus dose was detected in urine in 24 h [19]. In humans, there is evidence that renal excretion may be greater: 30% in 24 h in one study [20]. The use of rocuronium in patients with renal dysfunction has been reported; the results are conflicting. In a study of rocuronium 0.6 mg kg^{-1} in patients undergoing renal transplantation, onset and recovery times were similar to those of healthy patients [21]. Plasma clearance was similar in both groups, but volume of distribution at steady state was larger in renal patients (264 *vs* 207 ml kg^{-1} in healthy patients). This was thought to explain the longer elimination half-life of rocuronium in renal patients: 97 min compared with 71 min in healthy patients. Cooper and colleagues found longer mean recovery times after rocuronium 0.6 mg kg^{-1} in renal patients undergoing creation of an arteriovenous fistula, than in healthy patients, but this difference was not significant [22]. It is unlikely that rocuronium would produce such a reliable and predictable effect as atracurium in renal failure patients. For example, 25% of T1/T0 after rocuronium 0.6 mg kg^{-1} in renal patients varies from 35 to 115 min; in healthy patients the range is 32–60 min [22].

Unlike vecuronium [23], the metabolites of rocuronium do not have neuromuscular blocking activity [24] (fig. 1). Rocuronium may not have the unpredictable effects of vecuronium if used for prolonged infusion in critically ill patients undergoing intensive therapy: pharmacokinetic studies of rocuronium and its metabolites in such patients are needed.

Cirrhotic patients

The limited evidence on the effect of rocuronium in patients with hepatic cirrhosis is also conflicting [25, 26]. Rocuronium 0.6 mg kg^{-1} has been shown to have a more variable and prolonged effect in this disease state. In one of the two reported studies [25], a reduction in clearance was demonstrated in cirrhotic patients, but this was not statistically significant. In a larger study however, there was more convincing evidence of reduced clearance and prolonged recovery after rocuronium 0.6 mg kg^{-1} in cirrhotic patients [J. M. Hunter, personal communication].

Cardiovascular effects

Atracurium and vecuronium were developed in part to overcome the cardiovascular effects of the older non-depolarizing agents (even though anaesthetists often used these effects to advantage, e.g. hypotension produced by tubocurarine when it was desired to reduce arterial pressure or the sympathomimetic effect of pancuronium in hypovolaemic patients). These drugs are free of such direct cardiovascular effects, but this allows other agents used during anaesthesia to have an unmitigated action, for example the bradycardia produced by opioid analgesics or halothane. In ophthalmic or gynaecological procedures, reflex bradycardia is often detected if atracurium or vecuronium are used. In some, although not all, studies in which rocuronium was given, there was evidence of a slight vagolytic effect [27, 28]. This was not as marked as with pancuronium, but clinicians will realize that they are dealing with a different agent from vecuronium in this respect. Indeed, this feature of rocuronium may be attractive, especially for use in healthy patients during procedures where vagal stimulation commonly occurs, for example cholecystectomy. As with other aminosteroid neuromuscular blocking drugs, there is no evidence of histamine release after the use of rocuronium [28].

Thus rocuronium may be a useful adjunct for clinicians in specific areas of their practice. The onset of block is more rapid than with any other non-depolarizing neuromuscular blocking drug, but rocuronium has a duration of action which is at least as long as vecuronium. It may prove useful during that now rare event—general anaesthesia for Caesarean section [29]. But rocuronium is still not ideal: will Org 9487 one day fulfil the anaesthetist's desire for a rapid onset, rapid offset, non-depolarizing neuromuscular blocking drug [30]? This aminosteroid, which is undergoing clinical trials, is even less potent than rocuronium (ED_{90} 1.15 mg kg^{-1}). In addition to a rapid onset, it may be possible to antagonize the action of Org 9487 within a few minutes of administration. Will Org 9487 therefore become a replacement for suxamethonium? Read this journal for further developments in the field of neuromuscular pharmacology!

J. M. HUNTER
University Department of Anaesthesia
Royal Liverpool University Hospital
Liverpool L69 3BX

References

1. Hunter JM, Jones RS, Utting JE. Comparison of vecuronium, atracurium and tubocurarine in normal patients and in patients with no renal function. *British Journal of Anaesthesia* 1984; **56**: 941–950.
2. Hunter JM, Jones RS, Utting JE. Use of atracurium during general surgery monitored by the train-of-four stimuli. *British Journal of Anaesthesia* 1982; **54**: 1243–1250.
3. Foldes FF, Nagashima H, Nguyen HD, Schiller WS, Mason MM, Ohta Y. The neuromuscular effects of Org 9426 in patients receiving balanced anesthesia. *Anesthesiology* 1991; **75**: 191–196.
4. Bowman WC, Rodger IW, Houston J, Marshall RJ, McIndewar I. Structure: action relationships among some desacetoxy analogues of pancuronium and vecuronium in the anesthetized cat. *Anesthesiology* 1988; **69**: 57–62.
5. Paton WDM, Waud DR. The margin of safety of neuromuscular transmission. *Journal of Physiology* (*London*) 1967; **191**: 59–90.
6. Gramstad L, Lilleaasen P. Dose–response relation for atracurium, Org NC45 and pancuronium. *British Journal of Anaesthesia* 1982; **54**: 647–651.
7. Puhringer FK, Khuenl-Brady KS, Koller J, Mitterschiffthaler G. Evaluation of the endotracheal intubating conditions of rocuronium (Org 9426) and succinylcholine in outpatient surgery. *Anesthesia and Analgesia* 1992; **75**: 37–40.
8. Cooper R, Mirakhur RK, Clarke RSJ, Boules Z. Comparison of intubating conditions after administration of Org 9426 (rocuronium) and suxamethonium. *British Journal of Anaesthesia* 1992; **69**: 269–273.
9. Magorian T, Flannery KB, Miller RD. Comparison of rocuronium, succinylcholine, and vecuronium for rapid sequence induction of anesthesia in adult patients. *Anesthesiology* 1993; **79**: 913–918.
10. McCoy EP, Mirakhur RK, Maddineni VR, Wierda JMKH, Proost JH. The pharmacokinetics of rocuronium bromide after bolus and continuous infusion during halothane anaesthesia. *British Journal of Anaesthesia* 1996; **76**: 29–33.
11. Wright PMC, Caldwell JE, Miller RD. Onset and duration of rocuronium and succinylcholine at the adductor pollicis and laryngeal adductor muscles in anesthetized humans. *Anesthesiology* 1994; **81**: 1110–1115.
12. Cantineau JP, Porte F, d'Honneur G, Duvaldestin P. Neuromuscular effects of rocuronium on the diaphragm and adductor pollicis muscles in anesthetized patients. *Anesthesiology* 1994; **81**: 585–590.
13. Foldes F. Rapid tracheal intubation with non-depolarizing neuromuscular blocking drugs: the priming principle. *British Journal of Anaesthesia* 1984; **56**: 663.
14. Boyd AH, van Miert MM, Eastwood NB, Parker CJR, Hunter JM. Pharmacodynamics of rocuronium in patients with hepatic cirrhosis. *British Journal of Anaesthesia* 1994; **73**: 262P.
15. Agoston S, Crul P, Newton D, Bencini A, Boomsma P, Erdmann W. The neuromuscular blocking effects of Org NC 45, a new pancuronium derivative, in anaesthetized patients: a pilot study. *British Journal of Anaesthesia* 1980; **52**: 53S–59S.
16. Shanks CA, Fragen RJ, Ling D. Continuous intravenous infusion of rocuronium (ORG 9426) in patients receiving balanced, enflurane or isoflurane anesthesia. *Anesthesiology* 1993; **78**: 649–651.
17. Naguib M, Abdulatif M, Al-Ghamdi A. Dose–response relationships for edrophonium and neostigmine antagonism of rocuronium bromide (Org 9426)-induced neuromuscular blockade. *Anesthesiology* 1993; **79**: 739–745.
18. Lynam DP, Cronnelly R, Castagnoli KP, Canfell PC, Caldwell J, Arden J, Miller RD. The pharmacodynamics and pharmacokinetics of vecuronium in patients anesthetised with isoflurane with normal renal function or with renal failure. *Anesthesiology* 1988; **69**: 227–231.
19. Kheunl-Brady K, Castagnoli KP, Canfell PC, Caldwell JE, Agoston S, Miller RD. The neuromuscular blocking effects and pharmacokinetics of Org 9426 and Org 9616 in the cat. *Anesthesiology* 1990; **72**: 669–674.
20. Wierda JMKH, Kleef UW, Lambalk LM, Kloppenburg WD, Agoston S. The pharmacodynamics and pharmacokinetics of Org 9426, a new non-depolarizing neuromuscular blocking agent, in patients anaesthetized with nitrous oxide, halothane and fentanyl. *Canadian Journal of Anaesthesia* 1991; **38**: 430–435.
21. Szenohradszky J, Fisher DM, Segredo V, Caldwell JE, Bragg P, Sharma ML, Gruenke LD, Miller RD. Pharmacokinetics of rocuronium bromide (ORG 9426) in patients with normal renal function or patients undergoing cadaver renal transplantation. *Anesthesiology* 1992; **77**: 899–904.
22. Cooper RA, Maddineni VR, Mirakhur RK, Wierda JMKH, Brady M, Fitzpatrick KTJ. Time course of neuromuscular effects and pharmacokinetics of rocuronium bromide (Org 9426) during isoflurane anaesthesia in patients with and without renal failure. *British Journal of Anaesthesia* 1993; **71**: 222–226.
23. Segredo V, Caldwell JE, Matthay MA, Sharma ML, Gruenke LD, Miller RD. Persistent paralysis in critically ill patients after long-term administration of vecuronium. *New England Journal of Medicine* 1992; **327**: 524–528.
24. Muir AW, Houston J, Green KL, Marshall RJ, Bowman WC, Marshall IG. Effects of a new neuromuscular blocking agent (Org 9426) in anaesthetized cats and pigs and in isolated nerve–muscle preparations. *British Journal of Anaesthesia* 1989; **63**: 400–410.
25. Khalil M, D'Honneur G, Duvaldestin P, Slavov V, De Hys C, Gomeni R. Pharmacokinetics and pharmacodynamics of rocuronium in patients with cirrhosis. *Anesthesiology* 1994; **80**: 1241–1247.
26. Magorian T, Wood P, Caldwell J, Fisher D, Segredo V, Szenohradszky J, Sharma M, Gruenke L, Miller R. The pharmacokinetics and neuromuscular effects of rocuronium bromide in patients with liver disease. *Anesthesia and Analgesia* 1995; **80**: 754–759.
27. Mellinghoff H, Diefenbach Ch, Buzello W. Neuromuscular and cardiovascular properties of Org 9426. *Anesthesiology* 1991; **75**: A807.
28. Levy JH, Davis GK, Duggan J, Szlam F. Determination of the hemodynamics and histamine release of rocuronium (Org 9426) when administered in increased doses under N_2O/O_2–sufentanil anesthesia. *Anesthesia and Analgesia* 1994; **78**: 318–321.
29. Abouleish E, Abboud T, Lechevalier T, Zhu J, Chalian A, Alford K. Rocuronium (Org 9426) for Caesarean section. *British Journal of Anaesthesia* 1994; **73**: 336–341.
30. Wierda JMKH, van den Broek L, Proost JH, Verbaan BW, Hennis PJ. Time course of action and endotracheal intubating conditions of Org 9487, a new short-acting steroidal muscle relaxant; a comparison with succinylcholine. *Anesthesia and Analgesia* 1993; **77**: 579–584.

British Journal of Anaesthesia 1996; **76**: 484–486

CLINICAL INVESTIGATIONS

Dose requirements, efficacy and side effects of morphine and pethidine delivered by patient-controlled analgesia after gynaecological surgery

G. STANLEY, B. APPADU, M. MEAD AND D. J. ROWBOTHAM

Summary

We have compared the dose requirements and side effects of morphine with those of pethidine when administered by patient-controlled analgesia in 40 patients (ASA I–II, 20–65 yr) after elective total abdominal hysterectomy. Patients were allocated randomly, in a double-blind manner, to receive either morphine (bolus dose 2 mg, lockout time 10 min) or pethidine (bolus dose 20 mg, lockout time 10 min) for postoperative pain relief. Mean 24-h morphine and pethidine consumption was 70 (SEM 6.2) mg and 660 (67.8) mg, respectively (ratio 1:9.4). There were no significant differences in postoperative sedation, nausea, pain relief and patient satisfaction (VAS 0–100 mm), and requirements for antiemetics. Four patients receiving pethidine were withdrawn because of postoperative confusion and one receiving morphine because of intractable nausea and vomiting. The 95% confidence interval for this difference between the groups for VAS scores of sedation, nausea and pain were approximately 30 mm. (*Br. J. Anaesth.* 1996; **76**: 484–486)

Key words

Analgesia, postoperative. Analgesia, patient-controlled. Analgesics opioid, morphine. Analgesics opioid, pethidine.

Morphine and pethidine are used commonly for patient-controlled analgesia (PCA). There are some clinical situations where pethidine may be preferred to morphine, for example in asthmatics (anticholinergic action of pethidine) and after bowel anastomoses (dehiscence with morphine [1]) but the choice is often based on other perceived differences in efficacy and side effects such as quality of analgesia and tendency to nausea and vomiting. However, there are few data in the literature to enable proper comparison.

PCA enables comparison of the potency, efficacy and side effects of opioids in the treatment of pain after surgery [2, 3]. Therefore, we have examined, in a prospective, randomized, double-blind study, the relative efficacy and side effects of morphine and pethidine.

Patients and methods

We studied 40 patients, ASA I–II, aged 20–65 yr, undergoing total abdominal hysterectomy. All patients gave written informed consent to the study which was approved by the local Ethics Committee.

Patients were instructed in the use of the PCA machine (Graseby) on the day before surgery. A visual analogue scale (VAS) for assessment of nausea, pain and satisfaction was also explained. Each VAS comprised a 100-mm unmarked line, the ends of which denoted extremes of the variables in question, that is no nausea—extreme nausea; no pain—worst pain imaginable; very unhappy—delighted with everything.

All patients were premedicated with temazepam 10–20 mg orally, 1 h before surgery. Anaesthesia was induced with propofol 2 mg kg^{-1} and tracheal intubation and positive pressure ventilation were facilitated by the use of vecuronium 0.1 mg kg^{-1}. Anaesthesia was maintained with 1% isoflurane and 66% nitrous oxide in oxygen, and fentanyl 2–4 μg kg^{-1}.

Patients were allocated randomly (sealed envelopes) to receive morphine or pethidine by PCA (morphine 2 mg bolus, lockout 10 min; pethidine 20 mg bolus, lockout 10 min). The drug solution was prepared such that 1 ml contained either morphine 2 mg or pethidine 20 mg. The anaesthetist and nurse investigators were blinded to the contents of the PCA syringe. Operation of the PCA device was recorded by a printer (Hewlett–Packard Thermal Printer).

During the immediate recovery period, opioid was administered i.v. in a double-blind fashion in either 1-mg (morphine) or 10-mg (pethidine) increments in the recovery room. Increments were given every 2–4 min by the anaesthetist conducting the study, until pain control was judged to be comfortable and satisfactory by the patient. PCA was then commenced.

VAS scores for pain, nausea and satisfaction were made at 4, 8 and 24 h after commencing PCA. Sedation (wide awake—unable to stay awake) was also assessed at 4, 8 and 24 h by the blinded observers using a VAS scoring system. At the end of the 24-h study period, patients were asked to describe their appreciation of overall pain, nausea and vomiting which was assessed on a three-point verbal scale

---

G. STANLEY, FRCA, B. APPADU, MD, FRCA, M. MEAD, FRCA, D. J. ROWBOTHAM, MD, MRCP, FRCA, FFARCSI, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. Accepted for publication: December 1, 1995.

Correspondence to B.A.

(none/slight, moderate, severe). Patient satisfaction was assessed in a similar manner. All measurements were made by a blinded investigator. Prochlorperazine 12.5 mg i.m. was given for nausea on patient request by the nursing staff who were also blinded to the opioid used.

Data were analysed by Student's *t*-test, Mann–Whitney *U* test and chi-square test with Yates' correction, as appropriate. MANOVA for repeated measures was used for visual analogue scores.

Results

There were no significant differences in age, weight, temazepam premedication, duration of surgery and dose of fentanyl administered during surgery (table 1).

Mean 24-hour postoperative opioid consumption by PCA was morphine 70 (SEM 6.2) and pethidine 660 (67.8) mg (ratio 1 : 9.4). There were no significant differences between the groups in the VAS scores for pain, nausea, sedation or satisfaction, and these data, with 95% confidence intervals (CI) for the differences, are shown in table 2. There was no difference also in the number of doses of prochlorperazine administered (table 3).

Table 1 Patient characteristics (mean (SD or range)). No significant differences

	Morphine ($n = 20$)	Pethidine ($n = 20$)
Age (yr)	43 (20–65)	39 (25–49)
Weight (kg)	69.58 (13.16)	61.53 (7.43)
Temazepam (mg)	18.4 (3.8)	18.5 (4.8)
Duration of surgery (min)	65.79 (24.51)	66.00 (21.72)
Fentanyl (μg)	242 (53.40)	231 (43.30)

Table 2 Mean (SEM) and 95% confidence intervals for the differences in visual analogue scores for pain, nausea, sedation and satisfaction at 4, 8, 24 h

	Morphine (mm) ($n = 19$)	Pethidine (mm) ($n = 16$)	95% CI of difference
Pain			
4 h	45.2 (6.8)	55.9 (4.8)	(−6.9, 28.4)
8 h	42.4 (5.5)	44.4 (6.9)	(−15.7, 19.9)
24 h	39.7 (5.4)	40.3 (4.1)	(−13.5, 14.8)
Nausea			
4 h	14.7 (4.9)	11.9 (5.2)	(−17.4, 11.8)
8 h	31.0 (7.2)	37.1 (8.0)	(−15.8, 27.9)
24 h	33.1 (6.2)	27.1 (7.8)	(−26.0, 13.9)
Sedation			
4 h	67.2 (6.7)	65.3 (5.8)	(−20.2, 16.4)
8 h	50.2 (6.9)	55.7 (8.4)	(−16.4, 27.4)
24 h	55.8 (6.2)	48.2 (6.8)	(−26.3, 10.9)
Satisfaction			
4 h	52.1 (6.5)	69.2 (6.5)	(−34.9, 0.6)
8 h	48.2 (6.8)	61.1 (6.5)	(−28.8, 8.7)
24 h	69.3 (5.0)	63.1 (5.4)	(−21.1, 8.7)

Table 3 Number (%) of patients requiring prochlorperazine. No significant differences

Prochlorperazine doses (n)	Morphine ($n = 20$)	Pethidine ($n = 16$)
0	8 (40)	2 (13)
1	8 (40)	9 (56)
2	2 (10)	5 (31)
3	2 (10)	0 (0)

Table 4 Three-point verbal scoring at 24 h. No significant differences

	Morphine ($n = 20$)	Pethidine ($n = 20$)
Pain		
Severe	2	2
Moderate	8	10
Slight/none	10	8
Nausea		
Unbearable/severe	7	5
Moderate	8	9
Slight/none	5	6
Satisfaction		
Unhappy/miserable	9	5
Moderately happy	9	9
Happy/delighted	2	6

Overall pain, nausea and vomiting, and satisfaction scores obtained at the end of the study are shown in table 4. These data include those patients (see below) who were withdrawn from the study. There were no significant differences between the two groups.

Four patients in the pethidine group became disorientated and confused, 2–3 h after commencing PCA. They were withdrawn from the study and symptoms disappeared 2–3 h after removing PCA. There were no signs of respiratory depression, the maximum total amount of incremental pethidine received by these patients in the recovery room was 30 mg and overall no patient received more than 50 mg of pethidine in total.

One patient in the morphine group was withdrawn because of intractable nausea and vomiting. This patient became severely nauseated after receiving morphine 3 mg i.v. in the recovery room and was withdrawn from the study 3 h later. Her symptoms remained for several hours despite the use of prochlorperazine and ondansetron.

Discussion

We found no significant differences between morphine and pethidine PCA over a 24-h period in pain, nausea and vomiting, sedation and patient satisfaction. The 95% CI for the differences between the groups for VAS scores of pain, nausea and sedation were approximately 30 mm. The clinical importance of this difference is uncertain but we believe that it is unlikely to be significant. However, one patient was severely nauseated after a small dose of morphine and was withdrawn from study.

Our data are similar to those obtained in patients receiving morphine, pethidine or oxymorphone via PCA after elective Caesarean section during extradural anaesthesia [4]. Also, there were no differences between morphine and pethidine after open cholecystectomy [5]. The comparison in this study was less clear as its primary purpose was to investigate the efficacy and side effects of nalbuphine. However, there may be significant differences between morphine and pethidine when delivered via PCA in children [6]. Morphine was associated with better analgesia and greater sedation, with no other differences in side effects.

Morphine:pethidine potency ratios of between 1:10 and 1:12 have been described in the postoperative period [5,7,8]. Our ratio of 1:9.4 is consistent with these data.

While we did not intend to study postoperative confusion, it was interesting to note that four relatively young, healthy patients in our study became confused and disorientated in the early postoperative period after small doses of pethidine. This was not relieved by administration of oxygen, although there were no signs of respiratory depression, but improved rapidly after cessation of pethidine administration. Postoperative confusion with pethidine has been described previously. For example, in a recent well designed study of 245 postoperative patients, pethidine was associated significantly with postoperative delirium (odds ratio 2.7) [9]. However, these patients tended to be older than those in our study (> 50 yr) and psychological measurements were obtained from day 2 to day 5 after operation.

Confusion may be caused by norpethidine, a metabolite of pethidine [10]. However, in our study, significant plasma concentrations of this metabolite were unlikely as relatively small doses of pethidine were administered before symptoms commenced (maximum 50 mg). Many drugs with a central anticholinergic action are associated with deranged function of the central nervous system [11] and it may be that the anticholinergic action of pethidine was significant in our patients.

In conclusion, we have shown little difference in the pharmacodynamics of pethidine and morphine with respect to analgesia, nausea and vomiting, sedation and patient satisfaction using PCA with the regimen described in relatively healthy patients undergoing elective hysterectomy. However, our work gives further evidence to the view that pethidine may be associated with an increased incidence of postoperative confusion.

References

1. Aitkenhead AR, Robinson S. Influence of morphine and pethidine on the incidence of anastomotic dehiscence after colonic surgery. *British Journal of Anaesthesia* 1989; **63**: 230P.
2. Owen H, Mather LE, Rowley K. The development and clinical use of patient-controlled analgesia. *Anaesthesia and Intensive Care* 1988; **16**: 437–446.
3. Robinson SL, Rowbotham DJ, Smith G. Morphine compared with diamorphine. A comparison of dose requirements and side-effects after hip surgery. *Anaesthesia* 1991; **46**: 538–540.
4. Sinatra RS, Lodge K, Sibert K, Chung KS, Chung JH, Parker A, Harrison DM. A comparison of morphine, meperidine and oxymorphone as utilized in patient controlled analgesia following Cesarean section. *Anesthesiology* 1989; **70**: 585–590.
5. Bahar M, Rosen M, Vickers MD. Self administered nalbuphine, morphine and pethidine. Comparison, by intravenous route, following cholecystectomy. *Anaesthesia* 1985; **40**: 529–532.
6. Vetter TR. Pediatric patient-controlled analgesia with morphine versus meperidine. *Journal of Pain Symptom Management* 1992; **7**: 204–208.
7. Tyler DC, Krane EJ. Postoperative pain management in children. *Anesthesiology Clinics of North America* 1989; **7**: 155–170.
8. Tamsen A, Hartvig P, Fagerlund C, Dahlström B, Bondesson U. Patient controlled analgesia therapy: Clinical experience. *Acta Anaesthesiologica Scandinavica* 1982; (Suppl. 74): 157–160.
9. Marcantonio ER, Juarez G, Goldmann L, Mangione CM, Ludwig LE, Lind L, Katz N, Cook EF, Orav EJ, Lee TH. The relationship of postoperative delirium with psychoactive medications. *Journal of the American Medical Association* 1994; **272**: 1518–1522.
10. Armstrong PJ, Berston A. Normeperidine toxicity. *Anesthesia and Analgesia* 1983; **65**: 58–63.
11. Tune L, Holland A, Folstein M, Damlouji N, Garner T, Coyle JT. Association of postoperative delirium with raised anticholinergic drug levels. *Lancet* 1981; **328**: 651–652.

British Journal of Anaesthesia 1996; **76**: 487–491

Postoperative analgesia by continuous extradural infusion of ropivacaine after upper abdominal surgery†

S. A. Schug, D. A. Scott, J. Payne, P. H. Mooney and B. Hägglöf

Summary

Ropivacaine is a new local anaesthetic with advantages that suggest an important role in the provision of postoperative analgesia. The main aim of this study was to investigate the dose–response relationship of extradural infusion of ropivacaine. We studied 36 ASA I–III patients undergoing upper abdominal surgery during general anaesthesia and extradural block (catheter insertion at T6–9) using 0.5% ropivacaine in a randomized, double-blind study. After surgery nine patients each received an extradural infusion of either ropivacaine 0.1%, 0.2%, 0.3% or saline at a rate of 10 ml h^{-1} for 21 h. All patients had access to i.v. morphine via a PCA device. The ropivacaine groups consumed significantly less morphine over the 21-h infusion period than the saline group (medians: saline 75 mg; 0.1% ropivacaine 32 mg; 0.2% ropivacaine 39 mg; 0.3% ropivacaine 13 mg) ($P < 0.05$). Pain (VAS scores) at rest was significantly lower in all ropivacaine groups than in the saline group after 4 h of infusion (medians: saline 45 mm; 0.1% ropivacaine 15 mm; 0.2% ropivacaine 12 mm; 0.3% ropivacaine 0 mm). Pain on coughing was significantly less in all ropivacaine groups than in the saline group after 4 h infusion (medians: saline 67 mm; 0.1% ropivacaine 44 mm; 0.2% ropivacaine 33 mm; 0.3% ropivacaine 0 mm) and for 0.2% and 0.3% ropivacaine at later times. Motor block was negligible throughout the infusion. Patient satisfaction was higher in the 0.2% and 0.3% ropivacaine groups than in the two other groups. (*Br. J. Anaesth.* 1996; **76**: 487–491)

Key words

Anaesthetics local, ropivacaine. Anaesthetic techniques, extradural. Analgesia, postoperative. Surgery, abdominal.

Ropivacaine is a new, long-acting local anaesthetic, chemically homologous to bupivacaine and mepivacaine. It is the first enantiomerically pure local anaesthetic and exists as the *S*-enantiomer. In preclinical studies, ropivacaine produced less central nervous system and cardiac toxicity than bupivacaine [1]. Furthermore, in healthy volunteers, ropivacaine was less likely than bupivacaine to precipitate central nervous system and cardiovascular changes after i.v. infusion [2]. Data from studies in healthy volunteers and patients suggest that motor block with ropivacaine is less intense and of shorter duration than that with bupivacaine, while onset, duration and extent of sensory block are similar [3–7]. Based on these differences, ropivacaine may be better suited than bupivacaine to postoperative extradural analgesia after major surgery. The aim of the study was to investigate the dose–response relationship of ropivacaine for postoperative analgesia after upper abdominal surgery.

Patients and methods

After obtaining Institutional Ethics Committee approval and written informed consent, we studied patients undergoing abdominal surgery with an incision predominantly above the umbilicus in a double-blind, randomized study. Patients were aged 18–75 yr, ASA I–III, with weights 50–110 kg. Patients were excluded if they had contraindications to extradural anaesthesia or any significant medical history or concomitant disease which would influence postoperative assessments.

Premedication comprising temazepam 10–20 mg was given to most patients. After administration of a crystalloid solution of at least 500 ml, an extradural catheter was inserted 4–5 cm cephalad into the extradural space at T6–9. Five minutes after administration of a 3-ml test dose of 0.5% ropivacaine a 3–7-ml main dose was administered over 5 min. If sensory block to pinprick did not reach T6–4 within 30 min, an additional 5 ml of 0.5% ropivacaine was injected. Anaesthesia was then induced with thiopentone, neuromuscular block (vecuronium or atracurium), isoflurane and nitrous oxide in oxygen, and a maximum dose of fentanyl 200 µg. Additional boluses of 0.5% ropivacaine 5 ml were administered every 2 h during surgery or at signs of inadequate block, with a minimum interval of 30 min between injections. Additional boluses of fentanyl 50 µg were administered during surgery only when there was a

---

Stephan A. Schug*, MD, Julene Payne, MSc, Section of Anaesthetics, Department of Pharmacology and Clinical Pharmacology, University of Auckland, New Zealand. David A. Scott, MB, BS, FANZCA, Patricia H. Mooney, RN, Department of Anaesthesia, St Vincent's Hospital, Melbourne, Australia. Björn Hägglöf, PhD, Medical Department, Astra Pain Control AB, Södertälje, Sweden.

*Address for correspondence: Section of Anaesthetics, Department of Pharmacology and Clinical Pharmacology, School of Medicine, University of Auckland, Private Bag 92019, Auckland, New Zealand.

†Presented in part (poster) at the American Society of Anesthesiologists Annual Scientific Meeting, San Francisco, CA, USA, 1994.

need for additional analgesia. Patients who had surgery lasting more than 6 h were excluded from the study.

Within 1 h after the end of surgery, on arrival in the recovery room, an extradural infusion with either saline or 0.1%, 0.2% or 0.3% ropivacaine was commenced at a rate of 10 ml h^{-1} for 21 h (Abbott LifeCare Infuser, Abbott Laboratories, North Chicago, IL, USA). All patients had access to i.v. morphine via a patient-controlled analgesia (PCA) device (Abbott LifeCare PCA Infuser, Abbott Laboratories, North Chicago, IL, USA) with 1-mg bolus doses, 5 min lockout time and no dose limit. Allocation of patients to the study groups was randomized and double-blind.

Wound pain at rest and on coughing was assessed using a visual analogue scale (VAS) (0 mm = no pain; 100 mm = worst pain imaginable) and sensory block to pinprick, and motor block according to a modified Bromage scale (0 = no motor block; 1 = inability to raise extended legs; 2 = inability to flex knees; 3 = inability to flex ankle joints). These assessments were performed every 2 h from the end of surgery until 22:00 and hourly from 08:00 the following morning until return of normal sensation and motor function after discontinuation of the extradural infusion after 21 h; assessments were interrupted from 22:00 to 08:00 to enable patients to sleep overnight. PCA morphine consumption was recorded. Patients rated the overall quality of the treatment on a four-point scale (1 = poor; 2 = fair; 3 = good, 4 = excellent) after 4, 8 and 21 h of infusion. Arterial pressure and heart rate were recorded every hour after operation. Hypotension was defined as a systolic arterial pressure less than 80 mm Hg or more than 30% decrease compared with baseline, hypertension as arterial pressure greater than 180 mm Hg systolic or 110 mm Hg diastolic, bradycardia as heart rate less than 50 beat min^{-1} and tachycardia as heart rate greater than 120 beat min^{-1}. Other spontaneously reported or observed adverse events were recorded throughout the study.

This study was designed as the first dose-finding study of its type. Therefore, SD of relevant variables were not available and thus sample size could not be calculated. Ten patients per group were selected as it was thought that clinically relevant differences could be detected with this sample size. Data were compared in a pairwise manner using the two-tailed Wilcoxon rank sum test adjusted for centre. Differences were considered statistically significant at $P < 0.05$.

Results

We enrolled 50 patients. Eleven patients were withdrawn before commencement of the extradural infusion because of technical failure (three patients), inadequate block (T4–6 was not reached within 45 min after injection of the main dose in two patients), study violation (one patient) or change in surgical approach (five patients). Thirty-nine patients (21 enrolled at Auckland, 18 at Melbourne) were eligible for safety analysis (nine in the saline group and 10 in each of the ropivacaine groups). Three patients were withdrawn from efficacy analysis because of inoperable cancer or PCA or infusion pump failure, leaving nine patients in each of the four groups for efficacy analysis.

The groups were similar in age distribution, height, weight and ASA status, but there was a sex imbalance between groups (table 1). Surgery was mainly nephrectomy, splenectomy or gastrectomy. Catheter insertion, dose of ropivacaine and fentanyl for surgery, duration of surgery and time until commencement of the extradural infusion were also similar in the four groups (table 1).

MORPHINE CONSUMPTION

Figure 1 shows the median values of PCA morphine consumption over the 21 h of extradural infusion. All ropivacaine groups used significantly less morphine than the saline group ($P < 0.05$) and the difference between 0.3% and 0.1% ropivacaine was also significant ($P < 0.05$).

PAIN AT REST AND ON COUGHING

Median values for pain scores (VAS) at rest and on coughing are shown in figures 2 and 3 after 4, 8 and 21 h of infusion. Pain scores at rest were significantly lower in all ropivacaine groups than in the saline group after 4 h of infusion ($P < 0.05$). Pain scores at rest were also lower in the ropivacaine groups than in the saline group after 8 and 21 h of infusion, but this difference was not significant. Pain on coughing was significantly less in all ropivacaine groups than in the saline group after 4 h of infusion and for the 0.2% and 0.3% ropivacaine groups after 8 h ($P < 0.05$). After 21 h of infusion, pain scores on coughing were significantly lower in the 0.3% ropivacaine group than in the saline and 0.1% ropivacaine groups ($P < 0.05$), with no other significant differences between groups.

SENSORY AND MOTOR BLOCK

Sensory block regressed rapidly in the saline group (fig. 4). Upper spread in the ropivacaine groups was dose-dependent and remained stable throughout the infusion. The regression pattern was similar for lower spread in the saline and 0.1% ropivacaine groups. Lower spread remained stable in the 0.2% and 0.3% ropivacaine groups.

Motor block was not observed in the saline and 0.1% ropivacaine groups. One patient each in the 0.2% and 0.3% ropivacaine groups had motor block Bromage degree 1 and 2, respectively, after 4 and 8 h of infusion. After 21 h of infusion, one patient still had motor block degree 1 whereas the patient in the 0.3% ropivacaine group now had motor block degree 3.

QUALITY OF TREATMENT

The proportion of patients rating treatment as excellent at 4, 8 and 21 h of infusion is shown in figure 5. Patient satisfaction was significantly higher in the 0.2% and 0.3% ropivacaine groups compared

Table 1 Patient characteristics, duration of surgery and time to commencement of extradural infusion (mean (SD or range)), level of catheter insertion and doses of ropivacaine and fentanyl for surgery (median). S = Saline, R 0.1% = 0.1% ropivacaine, R 0.2% = 0.2% ropivacaine, R 0.3% = 0.3% ropivacaine

	Group			
	S ($n = 9$)	R 0.1% ($n = 10$)	R 0.2% ($n = 10$)	R 0.3% ($n = 10$)
Age (yr)	45 (19–73)	53 (37–70)	54 (34–71)	48 (18–75)
Height (cm)	171 (8)	171 (8)	170 (9)	162 (6)
Weight (kg)	78 (15)	77 (8)	79 (13)	69 (13)
Sex (M/F)	6/3	5/5	8/2	2/8
ASA I/II/III	4/5/0	2/7/1	3/7/0	4/5/1
Duration of surgery (min)	117 (57)	89 (51)	113 (37)	133 (49)
Time from end of surgery until start of infusion (min)	21 (10)	27 (11)	19 (6)	18 (6)
Catheter level	T7–8	T8–9	T7–8	T7–8
Ropivacaine (mg)	75	75	75	85
Fentanyl (μg)	150	150	200	112

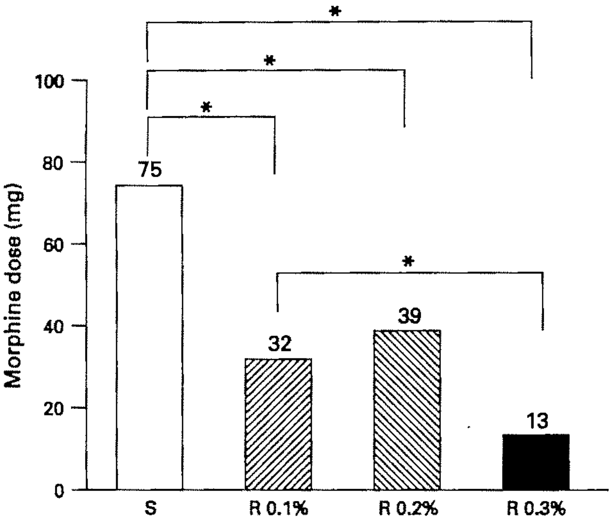


Figure 1 PCA morphine consumption. Median values over 21 h of extradural infusion of saline (S), 0.1% ropivacaine (R 0.1%), 0.2% ropivacaine (R 0.2%) or 0.3% ropivacaine (R 0.3%). $*P < 0.05$.

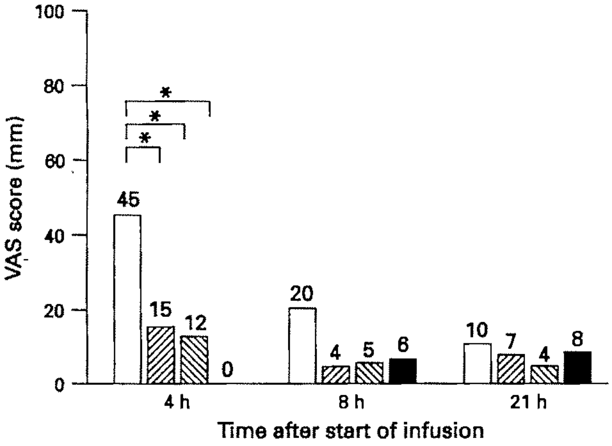


Figure 2 Pain (VAS scores) at rest. Median values at 4, 8 and 21 h of extradural infusion of saline (S) (□), 0.1% ropivacaine (R 0.1%) (▨), 0.2% ropivacaine (R 0.2%) (▧) and 0.3% ropivacaine (R 0.3%) (■). $*P < 0.05$.

with the saline group after 4 h of infusion ($P < 0.05$). Scores were also highest in these groups at 8 and 21 h (ns).

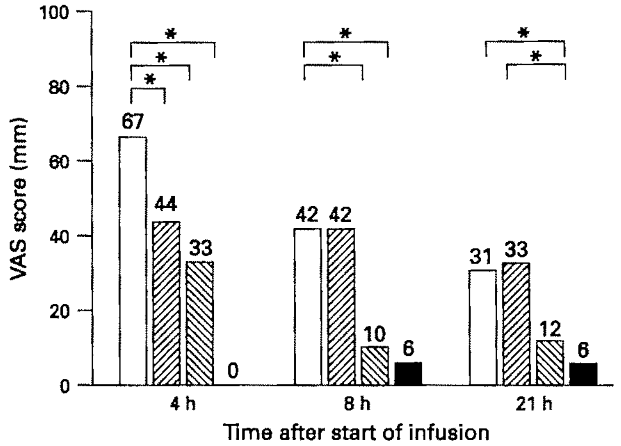


Figure 3 Pain (VAS scores) on coughing. Median values at 4, 8 and 21 h of extradural infusion of saline (S) (□), 0.1% ropivacaine (R 0.1%) (▨), 0.2% ropivacaine (R 0.2%) (▧) and 0.3% ropivacaine (R 0.3%) (■). $*P < 0.05$.

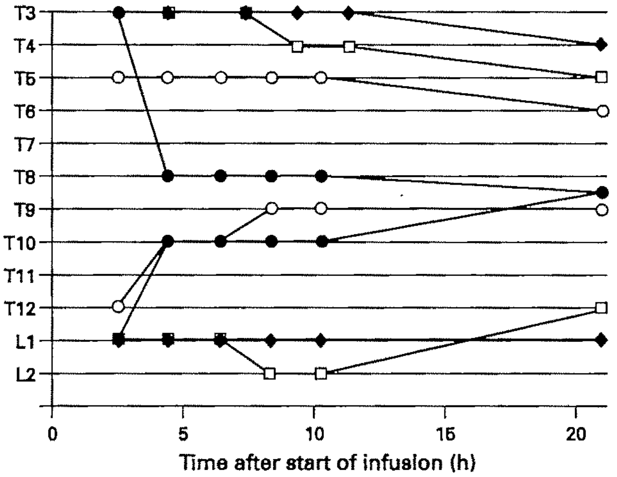


Figure 4 Sensory block(pinprick) from 2 h after start of infusion until the end of infusion in the saline (S) (●), 0.1% ropivacaine (R 0.1%) (○), 0.2% ropivacaine (R 0.2%) (□) and 0.3% ropivacaine (R 0.3%) (◆) groups.

ADVERSE EVENTS

Hypotension occurred more frequently in the 0.2% and 0.3% ropivacaine groups than in the two other groups, whereas pruritus and confusion/agitation

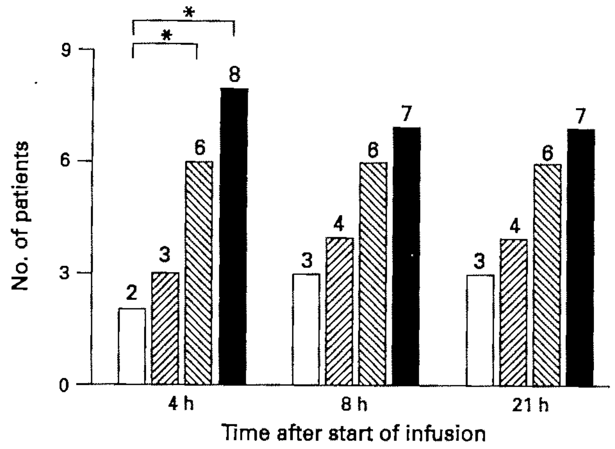


Figure 5 Proportion of patients (out of nine patients per group) with quality score excellent after 4, 8 and 21 h of extradural infusion of saline (S) (□), 0.1 % ropivacaine (R 0.1 %) (▨), 0.2 % ropivacaine (R 0.2 %) (▧) and 0.3 % ropivacaine (R 0.3 %) (■). $^*P < 0.05$.

Table 2 Six of the most common adverse events during 21 h of extradural infusion (number of patients). S = Saline, R 0.1 % = 0.1 % ropivacaine, R 0.2 % = 0.2 % ropivacaine, R 0.3 % = 0.3 % ropivacaine

	Group			
	S ($n = 9$)	R 0.1 % ($n = 10$)	R 0.2 % ($n = 10$)	R 0.3 % ($n = 10$)
Hypotension	0	1	4	5
Bradycardia	1	0	2	1
Nausea	5	0	6	7
Vomiting	2	0	2	1
Pruritus	1	0	0	0
Confusion/agitation	2	0	0	0

was observed only in the saline group. Other adverse events were equally distributed between the groups during extradural infusion, with the exception of nausea and vomiting (table 2). There was no difference in the incidence of nausea and vomiting in the saline and the two highest dose ropivacaine groups (0.2 % and 0.3 %), but there was no nausea or vomiting in the 0.1 % ropivacaine group. Most side effects were of a mild to moderate nature, except for two patients in the saline group who experienced severe nausea and vomiting and one who experienced severe confusion and agitation.

Discussion

This study was designed as a dose-finding study of ropivacaine for postoperative analgesia by extradural infusion; morphine consumption via PCA was the primary outcome measure. Overall morphine consumption in all ropivacaine groups was significantly lower than that of the saline group. The 0.3 % ropivacaine group showed the lowest morphine consumption. Even though all patients had free access to unrestricted i.v. morphine via a PCA device, initially patients in the saline group were unable to achieve sufficient pain relief at rest. These differences became even more striking for pain relief on coughing, where the 0.3 % ropivacaine group always had the lowest pain scores and the saline and 0.1 % ropivacaine groups never achieved median pain scores less than 30.

Therefore, the study showed that after upper abdominal surgery, extradural infusion of a local anaesthetic produced significantly superior analgesia at rest and on movement compared with systemic opioids alone. It confirms previous retrospective observations [8] and randomized trials [9], but to our knowledge for the first time in the form of a double-blind trial. That the superiority of extradural infusion becomes even more obvious during coughing is in agreement with the description of a "differential analgesic effect" of extradural local anaesthetics, as described by Dahl and colleagues [10]. It is noteworthy that even 0.1 % ropivacaine achieved good analgesia at rest, while only higher concentrations of ropivacaine produced a dense enough block to reduce pain on coughing. This is in accord with the hypothesis of an "extradural sieve" letting through more powerful stimuli at lower local anaesthetic concentrations [11]. From a clinical point of view, pain relief on coughing is most likely of relevance with regard to postoperative outcome. Ability to comply with physiotherapy and to mobilize early could reduce postoperative morbidity [12, 13], particularly after upper abdominal surgery where there may be a high rate of pulmonary complications [14].

In this context it is surprising that patients in the 0.3 % ropivacaine group used some morphine, despite high quality analgesia at all times. From interviews with these patients we conclude that some of this use was an expression of curiosity and boredom. Some patients used morphine for non-surgical aches and pains, such as sore throat from intubation and nasogastric tubes, or for deliberate sedation after hearing about an unexpected diagnosis of cancer. These observations and the inability of all patients to achieve comparable pain scores compromise the often recommended use of PCA as an "objective" pain measurement device [15, 16], but concur with those of other authors [17].

The results for spread of sensory block are in accord with morphine consumption and pain scores. The spread at the end of the infusion period (saline no segments, 0.1 % ropivacaine four segments, 0.2 % ropivacaine eight segments, 0.3 % ropivacaine 10 segments) was clearly dose-dependent and similar to the results obtained by extradural infusion in volunteers [4]. Near stable spreads throughout the infusion period in the 0.2 % and 0.3 % ropivacaine groups and sensory block regression in the 0.1 % ropivacaine group suggest inadequacy of the lower concentration to provide sufficient analgesia.

Motor block was minimal in our patients. We were surprised by one patient in the 0.3 % ropivacaine group who experienced a dense and persistent motor block; he may have suffered an accidental subdural catheter position as he also had the most widely spread sensory block [18], contradicting our own observations of thoracic extradural infusions in more than 1000 patients. The one patient in the 0.2 % ropivacaine group who initially showed a Bromage one block but then recovered, is in accord with our own experiences, that in some patients the initial intraoperative dense block may be maintained by the infusion for some time.

The adverse event which appeared to be attributable to the extradural infusion was hypotension, as its incidence increased in a dose-dependent manner. Nevertheless, the data presented here are in some way an over-representation of this adverse event, as the definition of hypotension in the study was very narrow. Therefore, situations which were often not regarded as hypotension clinically and did not require intervention were described as such. None of the reported hypotensive episodes was severe and those which needed correction were easily treatable by an increase in the i.v. infusion rate. The overall incidence of hypotension in the ropivacaine groups (33 %) was similar to that of 34 % described recently by Leith and colleagues with bupivacaine infusions [19].

All other adverse events occurred rarely or were distributed evenly across all groups. The incidence of nausea and vomiting was high even in the extradural infusion groups. This contradicts other observations of a low incidence of this side effect with extradural analgesia [8, 20], presumably because all of our patients also used some morphine as rescue medication. The absence of this adverse event in the 0.1 % ropivacaine group is probably coincidental. It is interesting that other typical adverse effects of systemic opioids, such as pruritus and confusion, occurred only in the saline group with the highest opioid consumption. Problems with urinary retention could not be assessed as all patients had a urinary catheter *in situ* as part of their surgical management.

Patient satisfaction was also clearly dose-dependent with the lowest scores in the saline group and the highest scores in the 0.3 % ropivacaine group at all times. This confirms our own experience that satisfaction scores are a sensitive tool for assessing postoperative analgesia [21]. The findings contradict the general assumption that patients are most satisfied with PCA as it offers the initial psychological advantage of putting patients in control [22, 23]. Obviously patients value highly significantly better analgesia, which confirms, in a double-blind design, observations published previously [8, 24].

Acknowledgements

This study was funded by a grant from Astra Pain Control AB, Södertälje, Sweden.

References

1. Feldman HS. Toxicity of local anaesthetics agents. In: Rice SA, Fish KJ, eds. *Local Anesthetic Toxicity*. New York: Raven Press, 1994; 107–133.
2. Scott DB, Lee A, Fagan D, Bowler GMR, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesthesia and Analgesia* 1989; **69**: 563–569.
3. Zaric D, Axelsson K, Nydahl PA, Philipsson L, Larsson P, Jansson JR. Sensory and motor blockade during epidural analgesia with 1.0 %, 0.75 % and 0.5 % ropivacaine—a double-blind study. *Anesthesia and Analgesia* 1991; **72**: 509–515.
4. Zaric D, Axelsson K, Nydahl PA, Philipsson L, Samuelsson L. Sensory and motor blockade during continuous epidural infusion of ropivacaine 0.1 %, 0.2 % and 0.3 % in volunteers—a double-blind study. *Regional Anesthesia* 1994; **19**(Suppl 2S): 60.
5. Kerkkamp HEM, Gielen, MJM , Edström HH. Comparison of 0.75 % ropivacaine with epinephrine and 0.75 % bupivacaine with epinephrine in lumbar epidural anesthesia. *Regional Anesthesia* 1990; **15**: 204–207.
6. Brockway MS, Bannister J, McClure JH, McKeown D, Wildsmith JAW. Comparison of extradural ropivacaine and bupivacaine. *British Journal of Anaesthesia* 1991; **66**: 31–37.
7. Brown DL, Carpenter RL, Thompson GE. Comparison of 0.5 % ropivacaine and 0.5 % bupivacaine for epidural anesthesia in patients undergoing lower-extremity surgery. *Anesthesiology* 1990; **72**: 633–636.
8. Schug SA, Fry RA. Continuous regional analgesia in comparison with intravenous opioid administration for routine postoperative analgesia. *Anaesthesia* 1994; **49**: 528–532.
9. Seeling W, Bothner U, Eifer B, Rockemann M, Schreiber M, Schurmann W, Steffen P, Zeininger A. Patient-controlled versus epidural analgesia using bupivacaine–morphine following major abdominal surgery. *Anaesthesist* 1991; **40**: 614–623.
10. Dahl JB, Rosenberg J, Hansen BL, Hjortso NC, Kehlet H. Differential analgesic effects of low-dose epidural morphine and morphine–bupivacaine at rest and during mobilization after major abdominal surgery. *Anesthesia and Analgesia* 1992; **74**: 362–365.
11. Crawford JS. The epidural sieve and MBC (minimal blocking concentration): an hypothesis. *Anaesthesia* 1976; **31**: 1277–1280.
12. Wiedemann B, Leibe S, Katzel R, Grube U, Landgraf R, Bierwolf B. The effect of combination epidural analgesia techniques in upper abdominal surgery on the stress reaction, pain control and respiratory mechanics. *Anaesthesist* 1991; **40**: 608–613.
13. Thomas JA, McIntosh JM. Are incentive spirometry, intermittent position pressure breathing and deep breathing exercises effective in the prevention of postoperative pulmonary complications after upper abdominal surgery? A systematic overview and meta-analysis. *Physical Therapy* 1994; **74**: 3–10.
14. Hall JC, Tarala RA, Hall JA, Mander J. A multivariate analysis of the risk of pulmonary complications after laparotomy. *Chest* 1991; **99**: 923–927.
15. Sechzer PH. Objective measurement of pain. *Anesthesiology* 1968; **29**: 209–210.
16. Lehmann KA. Einsatzmoeglichkeiten der On-demand-Analgesie fuer wissenschaftliche Fragestellungen. In: Lehmann KA ed. *Der postoperative Schmerz*. Berlin: Springer Verlag, 1990; 252–257.
17. Vickers M. Clinical trials of analgesic drugs. In: Harmer M, Rosen M, Vickers M, eds. *Patient-Controlled Analgesia*. London: Blackwell Scientific Publications, 1985; 42–50.
18. Boys JE, Norman PF. Accidental subdural analgesia: A case report, possible clinical implications and relevance to "massive extradurals". *British Journal of Anaesthesia* 1975; **47**: 1111–1113.
19. Leith S, Wheatly RG, Jackson IJ, Madej TH, Hunter D. Extradural infusion analgesia for postoperative pain relief. *British Journal of Anaesthesia* 1994; **73**: 552–558.
20. Wattwil M, Thoren T, Hennerdal S, Garvil J-E. Epidural analgesia with bupivacaine reduces postoperative paralytic ileus after hysterectomy. *Anesthesia and Analgesia* 1989; **68**: 353–358.
21. Schug SA, Dijkhuizen M, Russell K, Tester P. Dose finding studies on the combination of bupivacaine and low-dose fentanyl for postoperative epidural infusion. *Abstracts 7th World Congress on Pain*. Seattle: IASP Publications, 1993; 135–136.
22. Bowers KS. Pain, anxiety and perceived control. *Journal of Clinical Psychology* 1968: **32**: 596–602.
23. Kluger MT, Owen H. Patient's expectations of patient-controlled analgesia. *Anaesthesia* 1990; **45**: 1072–1074.
24. Egan KJ, Ready LB. Patient satisfaction with intravenous PCA or epidural morphine. *Canadian Journal of Anaesthesia* 1994; **41**: 6–11.

British Journal of Anaesthesia 1996; **76**: 492–498

Is there implicit memory after propofol sedation?

R. C. CORK, J. F. HEATON, C. E. CAMPBELL AND J. F. KIHLSTROM

Summary

Recent evidence indicates that implicit memory may be preserved during general anaesthesia. We tested for the presence of explicit and implicit memory in patients undergoing surgical procedures with local or regional anaesthesia and sedation with propofol. Initial i.v. boluses of propofol 0.5 mg kg^{-1} and fentanyl 1 µg kg^{-1} were administered, followed by an infusion of propofol 50 µg kg^{-1} min^{-1}. Administration of one or more doses of propofol 30 mg i.v. during operation was controlled either by the patient or the anaesthetist. At the start of the last skin stitch, patients were presented with a list of 15 stimulus words and the most frequently associated response. The infusion was then discontinued. After 1 h in the recovery area, all patients were tested for free recall, free association, cued recall and recognition on the list presented during surgery (critical list) and a matched list not presented (neutral list). Data of all patients without free recall (explicit memory) were analysed with repeated-measures analysis of variance. Of 36 patients, five demonstrated free recall. For the remaining 31 patients, cued recall and recognition showed no evidence of explicit memory. However, the free association tests demonstrated significant priming. The mean number of critical free associations was 6.6 (SEM 0.4) compared with 5.5 (0.4) neutral free association ($P < 0.05$). In the absence of explicit memory, implicit memory persists after intraoperative sedation with propofol. (*Br. J. Anaesth.* 1996; **76**: 492–498)

Key words

Anaesthetics i.v., propofol. Memory. Anaesthesia, depth.

Memory during anaesthesia has been classified into two different types: explicit and implicit [1]. Explicit memory involves conscious recollection of some previous episode and is what most of us understand as recall during anaesthesia. Implicit memory, however, refers to any effect on a person's experience, thought or action that is attributable to a past event, even if that person does not remember the event. Evidence for implicit memory during general anaesthesia has been controversial [2–4]. Although there is some concern that implicit memory may be spared despite profound impairment in explicit memory, different investigations have yielded different results, even in the same laboratory. For example, we have found that in surgical patients, implicit memory can be preserved during general anaesthesia with a pure oxygen–isoflurane technique [5]. However, using the same programme, we have found that implicit memory is not preserved during nitrous oxide–sufentanil anaesthesia [6]. It is difficult to draw conclusions from other available evidence, however, because of the heterogeneity in the anaesthetic programmes and memory tasks used. The difficulties of research in this area are compounded by the fact that we lack reliable, accurate measures of depth of anaesthesia. Recent investigations of non-patient volunteers found implicit memory preserved only at subanaesthetic concentrations of isoflurane [7] or nitrous oxide [8]. In our study involving anaesthetic concentrations of isoflurane, explicit memory did not occur in any of the patients [5].

Sedative drugs, such as the benzodiazepines, produce profound impairment of explicit memory, but they may spare implicit memory [9–11]. For example, in studies of non-patient volunteers, midazolam impaired recognition memory (a test of explicit memory), but spared priming effects in perceptual identification (a test of implicit memory) [12]. In a study using the same programme, it was found that propofol, a non-benzodiazepine sedative, also dissociated explicit and implicit memory; however, explicit memory was relatively unimpaired compared with midazolam [13]. Because the two drugs produced the same level of sedation, it appears that sedation *per se* does not necessarily impair memory. With the exception of this study, and some anecdotal evidence [14], the amnesic effects of propofol, as distinguished from its sedative effects, are unknown. In this study we tested for the presence of explicit and implicit memory in patients undergoing surgical procedures and sedation with propofol.

Patients and methods

After obtaining approval from the Louisiana State University Institutional Review Board and written informed consent, we studied patients undergoing

---

RANDALL C. CORK, MD, PHD, JOHN F. HEATON, MD, Department of Anesthesiology, Louisiana State University Medical Center, 1542 Tulane Ave, New Orleans, LA 70112, USA. CAROL E. CAMPBELL, MD, School of Nurse Anesthesiology, Charity Hospital/Xavier University, New Orleans, LA, USA. JOHN F. KIHLSTROM, PHD, Department of Psychology, Yale University, New Haven, CT, USA. Accepted for publication: November 21, 1995.

Correspondence to R.C.C.

Table 1 Sedation score

Responsiveness	
0	Asleep
1	No response to mild prodding or shaking
2	Response only after mild prodding or shaking
3	Response to name spoken loudly
4	Lethargic response to name spoken in normal tone
5	Immediate response to name spoken in normal tone
Speech	
0	Asleep
1	Few recognizable words
2	Slurring or prominent slowing
3	Mild slowing or thickening
4	Normal
Facial expression	
0	Asleep
1	Marked relaxation (slack jaw)
2	Mild relaxation
3	Normal
Ptosis	
0	Closed
1	Marked ptosis (half of the eye or more)
2	Mild ptosis (less than half of the eye)
3	No ptosis
Pain	
0	None
1	Mild
2	Moderate
3	Severe

ambulatory procedures involving local or regional anaesthesia with sedation. Exclusion criteria were ASA III or greater, allergy to propofol or soybeans, intellectual impairment or hearing difficulty. All patients were trained to "finger tap" as rapidly as possible on a counting device designed specifically for this study (by Joseph M. Moerschbaecher II, PhD, Professor and Head, Department of Pharmacology, LSU Medical Center).

No premedication was administered. Arterial systolic and diastolic pressures, heart rate, pulse oximetry, end-tidal $P\text{CO}_2$ ($P\text{E}'_{\text{CO}_2}$), and temperature were measured throughout the procedure. Before surgery, each patient was given a bolus dose of propofol 0.5 mg kg^{-1} i.v. and fentanyl 1 μg kg^{-1} i.v. The time taken for administration of each bolus was 5 s, and the second drug was given 5 min after the first. The order of administration of the two drugs was determined randomly. A constant infusion of propofol 50 μg kg^{-1} min^{-1} was given via a Bard InfusO.R. (C. R. Bard, Inc., North Reading, MA, USA) for all patients after the initial boluses of fentanyl and propofol. Patients were allocated randomly to receive supplementary boluses of propofol 30 mg during the procedure by one of two techniques: patient-controlled sedation (PCS) or anaesthetist-controlled sedation (ACS). PCS was carried out by the patient pushing a button attached to a demand pump (Bard Ambulatory PCA, C. R. Bard, Inc., North Reading, MA, USA). The patients were told to push the button whenever they wished to be "sleepier". ACS was carried out by the anaesthetist who was given instructions to sedate the patient to a responsiveness score of 4 and a speech score of 3 (see table 1). Clinical variables were recorded at the following events: (1) Baseline, before any drugs were given; (2) 2 min after the initial fentanyl bolus; (3) 2 min after the initial propofol bolus (the order of (2) and (3) were determined randomly); (4) 2 min after surgical incision; (5) at the last skin stitch; (6) on admission to the recovery room; and (7) 1 h after admission to the recovery room. Clinical variables included heart rate, arterial systolic and diastolic pressures, ventilatory frequency, $P\text{E}'_{\text{CO}_2}$ and haemoglobin saturation by pulse oximetry. $P\text{E}'_{\text{CO}_2}$ was not measured in the recovery room. At the same times, ordinal scores of pain reported by the patient, pain perceived by the anaesthetist, and sedation, as measured by scoring responsiveness, speech, facial expression and eye ptosis were allocated from the scale shown in table 1. In addition, the number of finger taps over a 10-s period were recorded. At the end of the procedure, total amounts of propofol, fentanyl and fluids administered were noted.

MEMORY TESTS

Four lists of paired associates developed by Kihlstrom were used for this experiment [15]. Each list consisted of 15 stimulus terms and the most frequent response given to each, as indicated by standard norms. For example, "boy—girl, man—woman, hammer—nail". The word pairs in the four lists were matched in terms of their normal stimulus–response probabilities. The probability of the correct response to a given cue averaged 0.51 for each list. Patients were allocated randomly to listen to one presentation of either lists 1 and 2 (tape A) or lists 3 and 4 (tape B) at the start of the last skin stitch. Both words of each word pair were presented. There was a brief identical introduction to each tape recording: "Please listen to the following word pairs." This introduction was used to adjust volume by the research assistant. Neither the anaesthetist nor other operating room personnel could hear the tape which lasted 90 s. When the word lists had been presented, the infusion of propofol was discontinued and no further administration was permitted.

Postoperative interviews were conducted 1 h after admission to recovery. By this time all patients were awake and responsive. The researcher who conducted the postoperative testing was not the same person who recorded the tape. In addition, this researcher did not know which paired associates had been played to the patient during surgery. The postoperative interviews comprised tests of free recall, cued recall and recognition for explicit memory, and free association for implicit memory. Patients were allocated randomly to receive one of two test sequences during the postoperative interview. Both test sequences included identical questions for free recall and recognition. However, in order to provide for adequate counterbalancing, patients who were given test 1 were tested only on lists 1 and 3 for cued recall and lists 2 and 4 for free association, while those given test 2 were tested on lists 2 and 4 for cued recall and lists 1 and 3 for free association. In each case, the list presented during surgery was the *critical list*, while the list not presented was the *neutral list*. The order of testing was as follows:

Free recall. Patients were asked if they remembered hearing words during surgery. If not they were

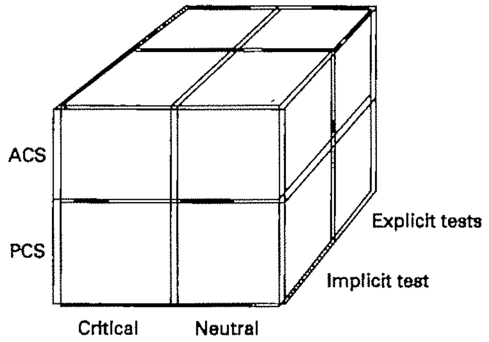


Figure 1 Experimental design. Independent variables are anaesthetist-controlled sedation (ACS) *vs* patient-controlled sedation (PCS), critical *vs* neutral list and implicit *vs* explicit tests. Analysis is with repeated-measures analysis of variance.

reminded that they had been read some words during surgery and were asked to recall any remembered items. A positive response was when patients remembered any of the words presented.

Free association. The cues were read to the patients in random order, and patients were asked to report the first word that came to mind. If no word came to mind, "none" was the accepted response. Patients were not forced to offer a word.

Cued recall. The patients were read the cues in random order and asked if any items reminded them of a word that had been presented during surgery. Again, "no" and/or "none" were acceptable responses. Guessing was discouraged.

Recognition. All 30 word pairs were read in random order and patients were asked to indicate those that had been read during surgery. "None" was an acceptable response and patients were discouraged from guessing.

The experimental design for tape and test is shown in figure 1. Key dependent variables were number of critical and neutral associates as measures of implicit memory (free association) and explicit memory (cued recall and recognition). The critical list of word pairs was played to the patient; the neutral list was not. Data were analysed with repeated measures analysis of variance. Within-subject effects examined were number of correct associations (critical *vs* neutral lists) and measure (free association, cued recall or recognition). The between-subject effect examined was sedation technique (PCS *vs* ACS). In addition, counterbalancing variables tested for potentially confounding effects were tape (A or B), test (1 or 2) and first drug bolus (fentanyl *vs* propofol). Comparison of clinical variables between those patients who demonstrated priming and those who did not was with Student's *t* test for grouped data. We accepted a result as significant if $P < 0.05$. All results for continuous variables are given as mean (SEM).

Results

Of the 36 patients studied, five (14%) demonstrated free recall (explicit memory) of words played on the tape. The analysis that follows focuses on those 31 patients with no free recall of any words on the tape. There were no differences in the results between tapes A and B or between tests 1 and 2. However, these comparisons were only for the complete group of 31 patients. Subgroups were not analysed because of the small number of patients. Table 2 lists the basic descriptive data for the 31 patients without recall, and table 3 the values of different variables collected during operation.

Table 2 Patient characteristics ($n = 31$) (mean (SEM) [range] or number (% of total))

Age (yr)	48 [20–83]
Sex (M/F)	9 (29%)/22 (71%)
Height (cm)	169 (2) [152–188]
Weight (kg)	79 (3) [40–110]
ASA	
I	7 (22.6%)
II	24 (77.6%)
Ethnic background	
Black	26 (83.9%)
White	3 (9.7%)
Hispanic	2 (6.5%)
Surgical procedure	
General surgery	17 (54.8%)
Orthopaedics	7 (22.6%)
Vascular	3 (9.7%)
Urology	4 (12.9%)
Regional anaesthesia	
Infiltration	23 (74.2%)
Spinal	6 (19.4%)
Bier block	2 (6.5%)

Table 3 Intraoperative variables ($n = 31$) (mean (SEM) [range]). SAP = Systolic arterial pressure, HR = heart rate

Duration of surgery (min)	49 (6) [8–175]
Duration of anaesthesia (min)	106 (9) [50–300]
Total propofol (mg)	279 (18) [75–525]
Fluids (ml)	913 (74) [200–1700]
Highest SAP (mm Hg)	164 (5) [120–212]
Highest HR (beat min^{-1})	83 (2) [60–118]
Lowest SAP (mm Hg)	113 (3) [80–142]
Lowest HR (beat min^{-1})	67 (2) [42–90]

CLINICAL, PAIN AND SEDATION VARIABLES

Clinical variables, including arterial systolic and diastolic pressures, ventilatory frequency, PE'_{CO_2} and haemoglobin saturation by pulse oximetry, are shown in table 4 for the events studied, including baseline, fentanyl bolus, propofol bolus, incision, last stitch, recovery admission and recovery discharge. There was no difference between patients receiving ACS or PCS in clinical variables or in the amount of propofol used (250 (30) mg for ACS *vs* 300 (30) mg for PCS). Heart rate, arterial systolic and diastolic pressures, ventilatory frequency and saturations exhibited significant time effects ($P < 0.05$), but PE'_{CO_2} did not change significantly throughout the procedure. Heart rate was greater, and arterial systolic and diastolic pressures and ventilatory frequency less at the last stitch, when the tape was played, compared with recovery at 1 h, when the interview was conducted ($P < 0.05$). Heart rate, arterial pressures and ventilatory frequency were all less when the tape was played compared with baseline ($P < 0.05$).

Ordinal scores of pain and consciousness are

Table 4 Clinical variables (mean (SEM)). HR = Heart rate, SAP = systolic arterial pressure, DAP = diastolic arterial pressure, f = ventilatory frequency. Order of initial fentanyl and propofol was determined randomly. Fentanyl and propofol results include all patients, irrespective of which drug was given first. *$P < 0.05$ compared with baseline and recovery (1 h)

	Baseline	Fentanyl (2 min)	Propofol (2 min)	Incision (2 min)	Last stitch (tape)	Recovery admission	Recovery (1 h)
HR (beat min^{-1})	78 (3)	76 (2)	76 (2)	72 (3)	73 (2)*	71 (2)	67 (2)
SAP (mm Hg)	153 (5)	150 (5)	138 (5)	139 (5)	124 (3)*	126 (3)	131 (3)
DAP (mm Hg)	82 (3)	79 (3)	74 (3)	74 (3)	69 (2)*	70 (2)	73 (2)
f (bpm)	17 (1)	15 (1)	15 (1)	17 (1)	15 (1)*	18 (1)	18 (1)
PE'_{CO_2} (kPa)	5.2 (0.2)	5.2 (0.2)	5.2 (0.2)	5.3 (0.2)	5.1 (0.2)	—	—
Saturation (%)	98.8 (0.2)	98.0 (0.4)	95.9 (0.7)	97.8 (0.3)	98.8 (0.3)	98.7 (0.2)	98.7 (0.2)

Table 5 Pain and consciousness variables (mean (SEM)). Finger tapping = number of taps/10 s; other scores based on ordinal scales in table 1. Order of administration of fentanyl and propofol was determined randomly. Fentanyl and propofol results include all patients, irrespective of which drug was given first

	Baseline	Fentanyl (2 min)	Propofol (2 min)	Incision (2 min)	Last stitch	Recovery admission	Recovery (1 h)
Pain reported (Patient)	0.03 (0.03)	0.03 (0.03)	0.00 (0.00)	0.26 (0.12)	0.06 (0.04)	0.13 (0.06)	0.29 (0.12)
Pain observed (Anaesthetist)	0.03 (0.03)	0.03 (0.03)	0.00 (0.00)	0.23 (0.10)	0.13 (0.06)	0.03 (0.03)	0.13 (0.08)
Finger tapping	37.4 (1.6)	28.9 (1.5)	21.8 (2.1)	25.0 (2.1)	23.3 (2.1)	35.1 (1.7)	38.1 (2.0)
Responsiveness	5.0 (0.0)	4.7 (0.1)	3.7 (0.2)	4.0 (0.2)	3.9 (0.2)	4.8 (0.1)	5.0 (0.0)
Speech	4.0 (0.0)	3.7 (0.1)	2.6 (0.2)	3.1 (0.1)	2.9 (0.2)	3.8 (0.1)	4.0 (0.0)
Facial expression	3.0 (0.0)	2.7 (0.1)	1.8 (0.2)	2.1 (0.1)	2.1 (0.1)	2.8 (0.1)	3.0 (0.0)
Ptosis	3.0 (0.0)	2.7 (0.1)	1.8 (0.2)	1.9 (0.2)	2.0 (0.2)	2.8 (0.1)	3.0 (0.0)

summarized in table 5 for the intraoperative and recovery periods. There was no difference between patients receiving ACS and PCS in pain or level of consciousness. Both pain reported by the patient and pain observed by the anaesthetist exhibited a time effect ($P < 0.05$), but neither pain score was significantly different from the other at any time. Finger tapping, responsiveness, speech, facial expression and eye ptosis revealed time effects ($P < 0.05$). As indices of sedation, these variables indicated an awake baseline, sedation after the initial dose of fentanyl and propofol, sedation at the last stitch and return to baseline by admission to the recovery area. These variables were significantly different between the last stitch, when the tape was played, and recovery at 1 h, when the tests for memory were performed ($P < 0.05$).

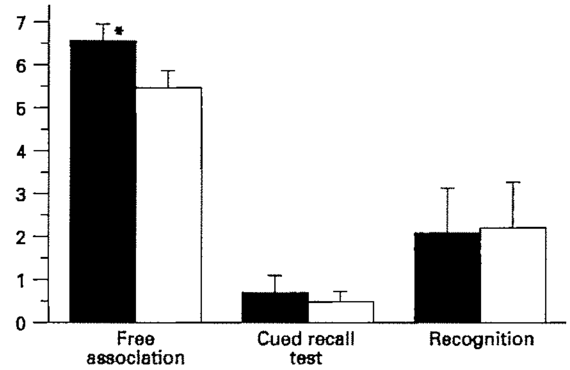


Figure 2 Critical (on tape) (■) and neutral (not on tape) (□) responses provided by the patient at the time of the postoperative interview. Critical responses were greater than neutral responses in the free association test ($P < 0.05$). Numbers of cued recall responses and word pair recognitions were not significantly different between the critical and neutral lists.

MEMORY

The results of five patients who demonstrated free recall were excluded from subsequent analysis, and the cued recall and recognition tests of the remaining 31 revealed no evidence of explicit memory. However, the results from the free association tests performed on the remaining 31 patients suggested implicit memory. Figure 2 shows the number of critical and neutral word pairs provided for each test at the time of the postoperative interview. Cued recall and recognition tests exhibited no difference between the number of critical and neutral word pairs provided as responses during the interview. In contrast, the number of critical free associations was 6.58 (0.36) compared with 5.48 (0.40) neutral free associations ($P < 0.05$). Figure 3 shows the distribution of the number of critical and neutral word pair free associations by number of patients. This shows that the difference detected was attributable to a small consistent difference in a number of patients, rather than extreme differences in a few patients. There were no effects attributable to the counterbalancing variables of tape (A *vs* B) or test (1 *vs* 2). There were also no effects from the initial drug (fentanyl *vs* propofol) or sedation technique (PCS *vs* ACS).

If we define priming as one or more critical responses than neutral responses, 20 of the 31 patients (64.5%) demonstrated priming. A number of clinical and sedation variables, most related to the response of the patient to the initial bolus of propofol,

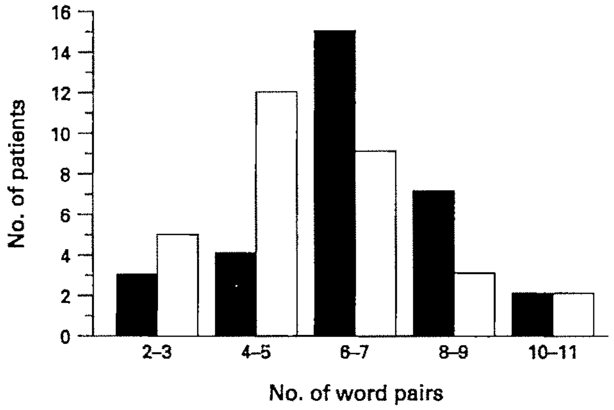


Figure 3 Distribution of the number of critical (■) and neutral (□) word pair free associations by number of patients. This shows that the difference detected was attributable to a small consistent difference between critical and neutral responses in a number of patients, rather than extreme differences in a few patients.

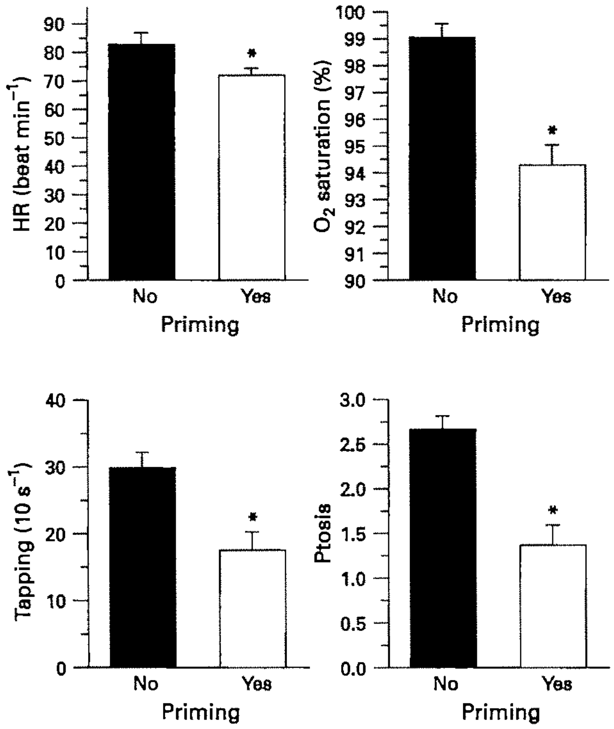


Figure 4 Variables after bolus administration of propofol which were different between those patients who subsequently demonstrated priming and those who did not. Priming was associated with lower heart rate (HR), decreased oxygen (O_2) saturation, slower finger tapping and lower ptosis scores (more ptosis) after the initial bolus of propofol 0.5 mg kg^{-1} ($P < 0.05$).

were associated with priming. Figure 4 shows the four variables which were significantly different between those patients who demonstrated priming and those who did not. Priming was associated with lower heart rate, decreased oxygen saturation, slower finger tapping and lower ptosis scores (more ptosis) after the initial bolus of propofol ($P < 0.05$). In addition to the difference in heart rate after propofol, mean heart rate was 72 (2) beat min^{-1} after the initial bolus of fentanyl for those patients who demonstrated priming, compared with 83 (4) beat min^{-1} for those who did not ($P < 0.05$).

Key variables not associated with priming were total propofol dose, time from the start of infusion and number of propofol boluses. There was no association between the dose of propofol administered and the priming response.

Discussion

This study has shown that patients who received sedation with propofol during surgery showed clear impairments in explicit memory. This was measured by free recall, cued recall and recognition of a list of paired associates presented during surgery. However, these patients also showed a priming effect on free association, which indicates that implicit memory was spared to some degree. This is the first study of ambulatory patients sedated with propofol to show preserved implicit memory, and it corroborates earlier results in non-patient volunteers [14].

For ACS *vs* PCS, our results differed from those of Osborne and colleagues [16] who studied the use of propofol with patient-controlled sedation in subjects undergoing bilateral extraction of third molar teeth during local anaesthesia. They found that patients controlling their own sedation (PCS) were less sedated than those receiving a propofol infusion by an anaesthetist. We found no difference in the level of sedation between ACS and PCS.

Our first two studies of implicit memory during general anaesthesia involved repeatedly playing the word lists to the patients from the first skin incision until the last skin stitch [5, 6]. We reasoned that the more repetitions played, the higher the likelihood of detecting implicit memory. However, a significant problem with this approach is that depth of general anaesthesia during surgery is variable and as yet unmeasurable, varying with both the amount of anaesthetic administered and surgical stimulation. It is possible that depth of anaesthesia during isoflurane–oxygen general anaesthesia (where preservation of implicit memory was demonstrated) varies more with surgical stimulation than depth of anaesthesia during nitrous oxide–sufentanil general anaesthesia (where preservation of implicit memory was not demonstrated).

To overcome this problem, first we used sedation, rather than general anaesthesia, so that we could measure depth by patient response. Second, we provided the patient with only one reading of the critical word pair list at exactly the same point in the procedure for each patient. These steps minimized the effect of varying anaesthetic depths, but neither solves the experimental problem. The solution, of course, is to develop a method of measuring depth of anaesthesia.

Our concerns about repetition enabling us to detect implicit memory are diminished by recent findings showing that repetition and duration of exposure to the stimulus seem to affect explicit but not implicit memory [17, 18]. Our results indicate that a single exposure is sufficient to alter postoperative behaviour. In addition, behaviour is altered in the absence of memory for the source of the suggested alteration in behaviour.

This is the first study of implicit memory that has found significant associations between the way in which patients respond to a drug and the degree of implicit memory. The responses noted, however, seem paradoxical. As shown in figure 3, those patients who later demonstrated implicit memory at the end of the procedure showed increased sensitivity to the initial bolus of propofol at the beginning of the procedure. Ptosis was more evident, and heart rate, oxygen saturation and number of finger taps in 10 s were more depressed by propofol in those patients who exhibited priming. Thus those patients who appeared to be more sedated after the initial bolus of propofol exhibited more implicit memory. There were no differences noted at the last skin stitch when the word pair tapes were played. This observation indicates that patient variability in response to sedation may also play a role in the variability of demonstrated implicit memory. In this case, a more sensitive CNS response to the initial dose of propofol was associated with subsequently increased implicit memory at a later time in the procedure.

Serum concentrations of propofol and dose–response examinations of the effect of different rates of propofol infusion on memory were not performed and EEG was not measured in this study. Our aim was to test for the presence of explicit and implicit memory in patients undergoing surgical procedures and sedation with propofol. Dose–response pharmacodynamic studies of implicit memory in a clinical situation are difficult. Under-sedating and over-sedating patients for a surgical procedure carry unwanted risks and repercussions.

EEG is neither a consistent nor precise measure of depth of anaesthesia. The EEG effects of propofol have been measured with a similar sedation programme by Veselis and colleagues [19]. EEG changes with increased power in the beta and delta frequency ranges were associated with propofol serum concentrations of 0.86 (0.04) $\mu g\ ml^{-1}$. A verbal learning task (Rey auditory–verbal learning task) administered before, during and after infusion demonstrated a marked reduction in short-term memory capacity and dramatically impaired free recall and recognition during infusion. This agrees with our results of inhibition of free recall, cued recall and recognition during infusion of propofol.

Chortkoff, Bennett and Eger observed significant implicit memory at 0.15 minimum alveolar concentration (MAC) of isoflurane in 10 volunteers [7]. At 0.28 MAC, statistical variance in response was greater than at 0.15 MAC, and with 10 observations, the power to detect a difference (if one existed) was compromised. This study and an earlier one by the same group [8] attempted to describe the pharmacodynamics of implicit memory by examining the degree of impairment as a function of drug dose. They found complete suppression of learning (both implicit and explicit) at less than 0.45 MAC of isoflurane in healthy volunteers not undergoing surgery. However, implicit memory may not be "well-behaved" pharmacodynamically because of the number of factors which may contribute to its existence. These include the physiological and psychological state of the patient, timing and degree of surgical stress, and timing and degree of sedation provided by the anaesthetist. Our study revealed no association between the dose of propofol administered and priming evidence of implicit memory.

There is some evidence that the degree of stress may play a role in the preservation of information. Exogenous catecholamines improve learning in anaesthetized rats [20]. Propofol-induced amnesia is impeded by amphetamine administration in mice [21]. Also several studies demonstrating learning during anaesthesia have used nitrous oxide [22–25], which has sympathetic stimulating properties. Our previous study with nitrous oxide also used a large dose of opioid which blunts the stress response. In contrast, our study with isoflurane–oxygen without nitrous oxide was probably a more stressful anaesthetic, because no opioids were given.

Why should propofol spare implicit memory in the absence of explicit memory? In common with the benzodiazepines, propofol interferes with normal hippocampal functioning [26]. Damage to hippocampal structures produces a profound anterograde amnesia affecting explicit memory, while leaving implicit memory intact [27]. Recent neuropsychological studies have provided evidence for a perceptual memory system which stores information about the form and structure, but not the meaning and function, of perceptual objects [28,29]. Hippocampal damage apparently leaves this system intact, permitting priming to occur in the absence of explicit memory. However, not all forms of implicit memory may be spared equally. For example, the literature on implicit memory distinguishes between repetition priming, which can be mediated by a perceptual representation system, and semantic priming, which requires that the meaning and the structure of the stimulus be analysed.

Repetition priming appears to be preserved during sedation for surgery (and, we believe, in certain cases of general anaesthesia for surgery also), but this sparing may not be extended to semantic priming, and other forms of implicit memory. Future studies of implicit memory during both general anaesthesia and sedation should use multiple measures of implicit memory, whose underlying cognitive mechanisms are known.

In theoretical terms, it is possible that propofol, in common with the benzodiazepines, may be used to create a pharmacological model for the study of the role of the hippocampus and other brain structures on memory [10]. But the sparing of implicit memory also has practical implications. Because propofol spares implicit memory, it is possible that surgical patients receiving sedation may be affected after operation by surgical events (such as untoward remarks made by medical personnel), even though they have no conscious recollection of these remarks. Anaesthetists and surgeons should not rely on sedation with propofol to abolish all traces of memory.

References

1. Schacter DL. Implicit memory: history and current status. *Journal of Experimental Psychology (Learning, Memory and Cognition)* 1987; **13**: 501–518.
2. Kihlstrom JF, Schacter DL. Anaesthesia, amnesia, and the

cognitive unconscious. In: Bonke B, Fitch W, Millar K, eds. *Memory and Awareness in Anaesthesia*. Amsterdam: Lisse, Swets & Zeitlinger, 1990; 21–44.

3. Kihlstrom JF. Implicit memory function during anesthesia. In: Sebel PS, Bonke B, Winograd E, eds. *Memory and Awareness in Anesthesia*. Englewood Cliffs: Prentice Hall, 1993; 10–30.
4. Ghoneim MM, Block RI. Learning and consciousness during general anesthesia. *Anesthesiology* 1992; **76**: 279–305.
5. Kihlstrom JF, Schacter DL, Cork RC, Hurt CA, Behr SE. Implicit and explicit memory following surgical anesthesia. *Psychological Science* 1990; **1**: 303–306.
6. Cork RC, Kihlstrom JF, Schacter DL. Absence of explicit or implicit memory in patients anesthetized with sufentanil/nitrous oxide. *Anesthesiology* 1992; **76**: 892–898.
7. Chortkoff B, Bennett H, Eger E. Subanesthetic concentrations of isoflurane suppress learning as defined by the category-example task. *Anesthesiology* 1993; **79**: 16–22.
8. Dwyer R, Bennett H, Eger E, Heilbron D. Effects of isoflurane and nitrous oxide in subanesthetic concentrations on memory and responsiveness in volunteers. *Anesthesiology* 1992; **77**: 888–898.
9. Ghoneim MM, Mewaldt SP. Benzodiazepines and human memory: a review. *Anesthesiology* 1990; **72**: 926–938.
10. Polster MR. Drug-induced amnesia: Implications for cognitive neuropsychological investigations of memory. *Psychological Bulletin* 1993; **114**: 477–493.
11. Bethune DW, Ghosh S, Gray B, Kerr L, Walker IA, Doolan LA, Sharples LD. Learning during general anaesthesia: Implicit recall after methohexitone or propofol infusion. *British Journal of Anaesthesia* 1992; **69**: 197–199.
12. Polster MR, McCarthy RA, O'Sullivan G, Gray PA, Park GR. Midazolam-induced amnesia: Implications for the implicit/explicit memory distinction. *Brain and Cognition* 1993; **22**: 244–265.
13. Polster MR, Gray PA, O'Sullivan G, McCarthy RA, Park GR. Comparison of the sedative and amnesic effects of midazolam and propofol. *British Journal of Anaesthesia* 1993; **70**: 612–616.
14. Wilson E, Mackenzie N, Grant IS. A comparison of propofol and midazolam by infusion to provide sedation in patients who receive spinal anaesthesia. *Anaesthesia* 1988; **43** (Suppl): 91–94.
15. Kihlstrom JF. Posthypnotic amnesia for recently learned material: Interactions with "episodic" and "semantic" memory. *Cognitive Psychology* 1980; **12**, 227–251.
16. Osborne GA, Rudkin GE, Jarvis DA, Young IG, Barlow J, Leppard PI. Intraoperative patient-controlled sedation and patient attitude to control. *Anaesthesia* 1994; **49**: 287–292.
17. Challis BH, Sidhu R. Dissociative effect of massed repetition on implicit and explicit measures of memory. *Journal of Experimental Psychology (Learning, Memory and Cognition)* 1993; **19**: 115–127.
18. Musen G. Effects of verbal labeling and exposure duration on implicit memory for visual patterns. *Journal of Experimental Psychology (Learning, Memory and Cognition)* 1991; **17**: 954–962.
19. Veselis RA, Reinsel RA, Wronski M, Marino P, Tong WP, Bedford RF. EEG and memory effects of low-dose infusions of propofol. *British Journal of Anaesthesia* 1992; **69**: 246–254.
20. Weinberger N, Gold P, Sternberg D. Epinephrine enables Pavlovian fear conditioning under anesthesia. *Science* 1984; **223**: 605–607.
21. Pang R, Quartermain D, Rosman E, Turndorf H. Effect of propofol on memory in mice. *Pharmacology, Biochemistry and Behavior* 1993; **44**: 145–151.
22. Levinson B. States of awareness during general anaesthesia. *British Journal of Anaesthesia* 1965; **37**: 544–546.
23. Bennett H, Davis H. Nonverbal response to intraoperative conversation. *British Journal of Anaesthesia* 1985; **57**: 174–179.
24. Evans C, Richardson P. Improved recovery and reduced post-operative stay after therapeutic suggestions during general anaesthesia. *Lancet* 1988; **2**: 491–493.
25. McLintock T, Aitken H, Downie C, Kenny G. Postoperative analgesic requirements in patients exposed to positive intraoperative suggestions. *British Medical Journal* 1990; **301**: 788–790.
26. Peduta VA, Concas A, Santoro G, Biggio G, Gessa GL. Biochemical and electrophysiologic evidence that propofol enhances GABAergic transmission in the rat brain. *Anesthesiology* 1991; **75**: 1000–1009.
27. Squire LR, Zola-Morgan S. The medial temporal lobe memory system. *Science* 1991; **253**: 1380–1386.
28. Schacter DL. Perceptual representation systems and implicit memory: Toward a resolution of the multiple memory systems debate. In: Diamond A, ed. The Development and Neural Bases of Higher Cognitive Functions. *Annals of the New York Academy of Sciences* 1990; **608**: 543–571.
29. Tulving E, Schacter DL. Priming and human memory systems. *Science* 1990; **247**: 301–306.

British Journal of Anaesthesia 1996; **76**: 499–502

Activation of the electrocorticogram by propofol during surgery for epilepsy

M. SMITH, S. J. SMITH, C. A. SCOTT AND W. F. J. HARKNESS

Summary

Propofol is used widely during general anaesthesia but there has been concern that it may be implicated in provoking seizure activity. We have investigated the effects of low-dose propofol on the electrocorticogram of anaesthetized patients undergoing surgery for medically intractable epilepsy. During continuous peroperative recording of the electrocorticogram, propofol was administered in 25 mg increments until burst suppression occurred. Activation of the electrocorticogram occurred in 17 of 20 patients. There was an increase in mean spike frequency in 16, extension of spike distribution in 15 and polyphasia in 13 patients. The mean dose of propofol required to cause burst suppression was 88.2 (range 25–175) mg. We conclude that at low doses, propofol caused activation of the electrocorticogram in epileptic patients but at higher doses burst suppression was induced. (*Br. J. Anaesth.* 1996; **76**: 499–502)

Key words

Anaesthetics i.v., propofol. Epilepsy. Monitoring, electrocorticography.

Propofol is used widely during general anaesthesia and for sedation in the intensive care unit. It is gaining popularity for neurosurgical anaesthesia [1] in part because it causes a dose-dependent decrease in intracranial pressure and cerebral metabolic rate and, at modest doses, cerebral perfusion pressure is maintained [2, 3]. It has a favourable pharmacokinetic profile which allows easy control of depth of sedation and rapid and predictable arousal. However, recently there has been concern that propofol may be implicated in provoking seizure activity and some avoid its use in epileptic patients. In contrast, it has been used successfully in the treatment of status epilepticus and appears to have no adverse effect in neurosurgical patients who are at "high risk" of developing seizure activity.

We have investigated the effect of propofol on the electrocorticogram (ECoG) of anaesthetized patients undergoing surgery for medically intractable epilepsy.

Patients and methods

The study was carried out with the approval of the Joint Medical Ethics Committee of the National Hospital for Neurology and Neurosurgery and Institute of Neurology. We studied 20 patients with medically intractable epilepsy. Premedication was omitted but anticonvulsant medication was continued into the perioperative period and administered on the morning of surgery. Anaesthesia was induced with thiopentone 4–5 mg kg^{-1}, fentanyl 1–3 μg kg^{-1} and vecuronium 0.15 mg kg^{-1}. The trachea was intubated and ventilation controlled to maintain Pa_{CO_2} at 3.8–4.2 kPa. Anaesthesia was maintained with isoflurane and 50% nitrous oxide in oxygen, and neuromuscular block was continued with infusion of vecuronium. Before recording the ECoG, the inspired isoflurane concentration was maintained at < 1 MAC to minimize anaesthetic-induced changes in the cortical EEG. Arterial pressure was controlled with incremental fentanyl (to a maximum of 8 μg kg^{-1}) and labetolol, and after ECoG recording by deepening anaesthesia with increased inspired isoflurane concentrations.

Heart rate, invasive arterial pressure (radial artery), oxygen saturation and end-tidal carbon dioxide and isoflurane concentrations were monitored continuously. Arterial blood-gas analysis was used to confirm arterial carbon dioxide tensions.

It is a standard part of the epilepsy surgical procedure at the National Hospital to carry out peroperative recording of epileptiform spiking with ECoG to determine the margins of surgical resection. Intraoperative ECoG for temporal lobectomy was recorded using a 25-contact (5 × 5) plate with an inter-contact spacing of 1 cm. The ECoG was recorded as an analogue signal using an 18-channel EEG machine (Nihon-Kohden). Two standard recording positions over the lateral convexity of the temporal lobe are used: anteriorly, with the first row of contacts approximately 1–2 cm behind the pole of the temporal lobe, and posteriorly, with the plate approximately 4 cm from the pole.

After diagnostic corticography, a 3-min period of baseline recording was obtained. Propofol was then administered i.v. in 25-mg increments, at 3-min intervals, until burst suppression occurred.

EEG spike analysis was performed manually before and after administration of propofol by one of the authors (S.J.S.). Activation of the ECoG was

---

MARTIN SMITH, MB, BS, FRCA (Department of Neuroanaesthesia); SHELAGH J. SMITH, BSC, MB, BS, FRCP, CATHERINE A. SCOTT, BSC, (Department of Neurophysiology); WILLIAM F. J. HARKNESS, FRCS (Department of Neurosurgery); The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG. Accepted for publication: December 5, 1995.

defined as: increase in the frequency of spiking; more extensive spike distribution; or polyphasic spikes. The frequency of spiking was taken as the average number of spikes in three randomly selected 20-s periods. The extent of spiking was assessed by counting the number of contacts at which spiking was seen. Extension was deemed to have occurred if spiking was present at two or more additional contacts after propofol. The Wilcoxon test for paired data was used to compare the frequency and extent of spike activity before and after administration of propofol.

Results

We studied seven males and 13 females, mean age 25.6 (range 18–38) yr and mean weight 71.1 (51–97) kg. The pathological diagnosis was hippocampal sclerosis ($n = 16$) or dysembryoplastic neuroepithelial tumour ($n = 4$) and the surgical procedures consisted of tailored temporal lobectomy (including excision of mesial temporal structures) or lesionectomy.

There were no changes in heart rate, arterial pressure, oxygen saturation or end-tidal carbon dioxide tension during the study. The mean dose of propofol required to cause burst suppression was 88.2 (range 25.0–175.0) mg and individual doses are shown in table 1.

Activation of the ECoG by propofol occurred in 17 of 20 patients (table 1). Examples of ECoG recordings with activation are shown in figure 1. Increase in mean spike numbers from 3.6 to 6.7 occurred in 16 patients ($P < 0.005$). There was extension of spike distribution from 3 to 10 contacts in 15 patients ($P < 0.005$) with marked extension

Table 1 ECoG activation after administration of propofol

Patient No.	Weight (kg)	Propofol dose (mg)	Increased in spike numbers	Extension of spike distribution	Development of polyphasia
1	65	75	+	+	+
2	73	50	+	+	+
3	53	50	+	+	+
4	72	75		Continuous spike activity	
5	54	50	+	+	+
6	82	25	+	+	−
7	79	50	−	+	+
8	81	100	+	+	+
9	71	50		Burst suppression by 20 s	
10	63	100	+	+	−
11	78	150	+	+	+
12	88	150	+	−	+
13	97	100	+	+	+
14	74	100	+	+	+
15	68	50	+	+	−
16	68	100	+	+	−
17	51	50		No spike activity	
18	88	175	+	−	+
19	58	75	+	+	+
20	59	100	+	+	+

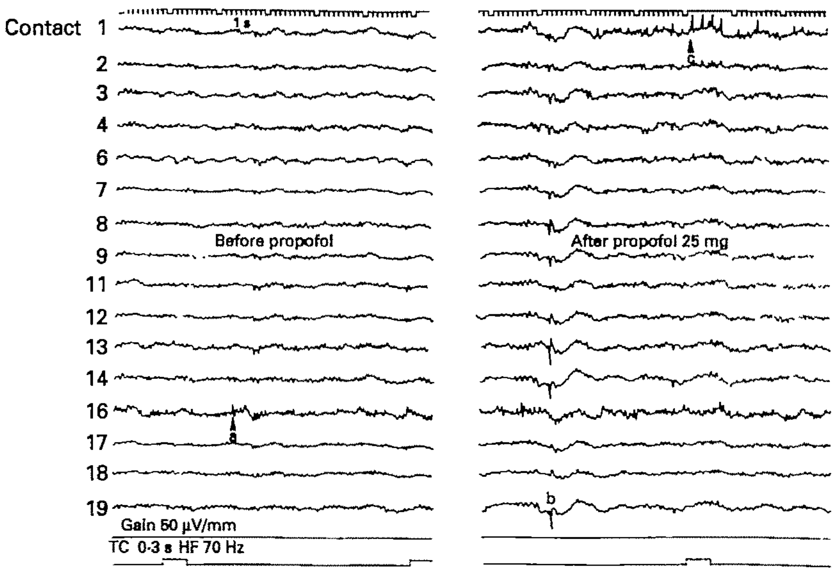


Figure 1 ECoG recording before and after administration of propofol. Before propofol, one epileptiform spike is noted at contact 16 (a). After propofol 25 mg, the epileptiform discharges become more widespread (b) and runs of spikes occur with polyphasia (c). The recording was common referential; same gain and filter settings were used before and after administration of propofol.

(spiking recorded from all contacts) in five. Polyphasia occurred in 13 patients. Ten patients developed a combination of increased spike frequency and distribution, and polyphasia after propofol (table 1).

Activation of the ECoG was not observed in three patients. In one there was continuous spike activity (1 s^{-1}) before and after administration of propofol but there was no change in spike morphology after propofol. In another, burst suppression occurred within 20 s of the initial 25-mg bolus of propofol and in the third there was no spiking before or after propofol administration.

Discussion

Activation of the ECoG by propofol was noted first by Hodkinson, Frith and Mee in 1987 [4]. They described an increase in the frequency of epileptiform spikes and the development of polyspikes, both within and beyond a previously mapped epileptogenic focus, after a bolus of propofol 2 mg kg^{-1}. At the clinical level, generalized seizures and opisthotonos have been attributed to propofol anaesthesia in patients with no previous neurological history and also in those with a history of epilepsy [5–8]. However, several of these case reports did not include EEG conformation of seizure activity and in one with contemporary EEG recording, a subcortical origin of the abnormal movements was postulated [8]. Other causes of seizure activity cannot be excluded in many of the reports. For example, propofol has been implicated as the cause of a grand mal seizure in a patient after termination of propofol sedation 5 days after deep hypothermic circulatory arrest [9]. The validity of implicating propofol as the cause of seizures in a case involving so many other factors has already been questioned [10]. There has however, been sufficient concern to cause the Committee on Safety of Medicine to issue a Safety Action Bulletin in 1992, drawing attention to the possible link between propofol and provocation of seizures [11].

Our results confirmed that, at low doses, propofol caused activation of the ECoG in epileptic patients. The activating effect may be dose related. In a study of propofol in 20 patients with indwelling subdural strip electrodes undergoing chronic monitoring as part of pre-surgical evaluation [12], only five showed induction of epileptiform activity. However, patients in this study received a minimum dose of propofol 50 mg followed by 70- or 140-mg increments, and spike induction occurred most frequently in those patients receiving the lower doses.

Burst suppression in the EEG is generally considered to be the end-point of the treatment of seizures or status epilepticus with anaesthetic agents. All patients in our study developed burst suppression at higher doses of propofol, except for one, in whom burst suppression occurred soon after the initial dose of propofol. Profound burst suppression after bolus administration of propofol (2 mg kg^{-1}) to patients receiving nitrous oxide in oxygen and sufentanil infusion, during anaesthesia for epilepsy surgery, was also noted in a recent study [13]. This study failed to demonstrate an increase in the frequency of interictal spikes, presumably because of the relatively large doses of propofol and the early onset of burst suppression.

Although an activating effect of propofol was observed in our study, it has been shown previously to have anticonvulsant effects in both animals [14–16] and humans. It has been used successfully in the treatment of status epilepticus resistant to other medical therapies [17, 18] and is known to shorten the duration of seizure activity during electroconvulsive therapy [19]. Additionally, many i.v. anaesthetic agents, which are anticonvulsants when given in the usual clinical dose (e.g. thiopentone), show proconsulvant activity at lower doses [20]. It appears likely from our data, and that of other workers [12], that propofol might also have dose-dependent pro- and anticonvulsant properties. In common with other i.v. anaesthetic agents, proconvulsant activity is seen at lower doses and anticonvulsant activity at higher doses.

In our study, the effects of propofol on the ECoG were evaluated during isoflurane anaesthesia and this may have affected the results. However, during the study the inspired concentration of isoflurane was < 1 MAC and it is possible to obtain high quality peroperative ECoG, with little or no apparent anaesthetic interference on the recording, using low-dose isoflurane [21, 22]. However, we are unable to comment on the combined ECoG effects of propofol and isoflurane. Adjuvants, such as opioids and nitrous oxide, cause EEG suppression at lower doses of isoflurane than might otherwise be anticipated [23]. Isoflurane may reduce or suppress background epileptiform activity and has been used successfully in the treatment of status epilepticus [24]. It is possible that isoflurane may in turn suppress the activating effects of propofol and our results may have underestimated the true extent of ECoG activation. The doses of propofol required to produce burst suppression in our patients were lower than normal anaesthetic doses. In one patient, burst suppression occurred within a few seconds of the initial 25-mg bolus of propofol and persisted for almost 15 min. If the presence of isoflurane influences the degree of ECoG change, we believe that its effect would be to reduce rather than enhance the activating effects of propofol.

All patients continued to receive their anticonvulsant medication during and after surgery and drug concentrations were measured before operation to ensure therapeutic concentrations. Although it is possible that the variety of preoperative medication might have altered the effects of propofol on the ECoG, it is again likely that these would minimize the activating effects of propofol. Rapid decreases in plasma concentrations of anticonvulsant medication may result in an increase in epileptiform spiking [25] but it is unlikely that plasma concentrations changed significantly during the study. Furthermore, activation of the ECoG was linked temporally to the administration of propofol. We believe, therefore, that activation of the ECoG observed during our study was related directly to the introduction of propofol.

Whether or not our findings are of clinical significance is a matter for debate. It is also uncertain if similar effects would be noted after administration of propofol to non-epileptic patients. It is conceivable however, that during induction or recovery from propofol anaesthesia or sedation, a stage of activation is passed as blood propofol concentrations increase or decrease through a critical plasma concentration. This may increase the risk of epileptiform activity, particularly in those already predisposed to seizures.

Propofol is often used for intracranial surgery during general anaesthesia and has become the agent of choice for sedation during awake craniotomy [22, 26]. Awake resection of epileptic foci is now commonplace in the USA and gaining popularity in the UK. Cortical mapping of epileptiform activity in awake and anaesthetized patients, and stimulation testing to identify eloquent areas in awake patients, allows careful identification of surgical resection margins. In view of the apparent activation of the ECoG by low doses of propofol, we would not recommend the use of propofol during general anaesthesia for epilepsy when the ECoG is used to guide tailored resection. When propofol is used as an adjunct to sedation during awake procedures, the infusion should be discontinued at least 30 min before cortical mapping with the ECoG.

References

1. Hoffman WE, Kochs E. Propofol: an intravenous anesthetic for neuroanesthetic practice? *Journal of Neurosurgical Anaesthesiology* 1992; 4: 75–77.
2. Artru AA, Shapira Y, Bowdle TA. Electroencephalogram, cerebral metabolic and vascular responses to propofol anesthesia in dogs. *Journal of Neurosurgical Anesthesiology* 1992; 2: 99–109.
3. Ramani R, Todd MM, Warner DS. A dose-response study of the influence of propofol on cerebral blood flow, metabolism and the electroencephalogram in the rabbit. *Journal of Neurosurgical Anesthesiology* 1992; 4: 110–119.
4. Hodkinson BP, Frith RW, Mee EW. Propofol and the electroencephalogram. *Lancet* 1987; 2: 1518.
5. Saunders PRI, Harris MNE. Opisthotonos and other unusual neurological sequelae after outpatient anaesthesia. *Anaesthesia* 1990; 45: 552–557.
6. Jones GW, Boykett MH, Klok M. Propofol, opisthotonos and epilepsy. *Anaesthesia* 1988; 43: 904.
7. De Friez CB, Wong HC. Seizures and opisthotonos after propofol anesthesia. *Anesthesia and Analgesia* 1992; 75: 630–632.
8. Borgeat A, Dessibourg C, Popovic V, Meier D, Blanchard M, Schwander D. Propofol and spontaneous movements: an EEG study. *Anesthesiology* 1991; 74: 24–27.
9. Au J, Scott DHT, Walker WS. Withdrawal syndrome after propofol. *Anaesthesia* 1990; 45: 741–742.
10. Grant IS, Worsley M. Withdrawal syndrome after propofol. *Anaesthesia* 1991; 46: 238.
11. Committee on Safety of Medicines. Propofol and delayed convulsions. *Current Problems* 1992; 35: 2.
12. Hufnagel A, Elger CE, Nadstawek J, Stoeckel H, Boker DK. Specific response of the epileptic focus to anaesthesia with propofol. *Journal of Epilepsy* 1990; 3: 37–45.
13. Ebrahim ZY, Schubert A, Van Ness P, Wolgamuth B, Awad I. The effect of propofol on the electroencephalogram of patients with epilepsy. *Anesthesia and Analgesia* 1994; 78: 275–279.
14. Lowson S, Gent JP, Goodchild CS. Anticonvulsant properties of propofol and thiopentone; comparison using two tests in laboratory mice. *British Journal of Anaesthesia* 1990; 64: 59–64.
15. Lowson S, Gent JP, Goodchild CS. Convulsive thresholds in mice during the recovery phase from anaesthesia induced by propofol, thiopentone, methohexitone and etomidate. *British Journal of Pharmacology* 1991; 102: 879–882.
16. De Riu PL, Petruzzi V, Testu C, Malas M, Melis F, Caria MA, Mameli O. Propofol anticonvulsant activity in experimental epileptic status. *British Journal of Anaesthesia* 1992; 62: 177–181.
17. Mackenzie SJ, Kapadia F, Grant IS. Propofol infusion for control of status epilepticus. *Anaesthesia* 1990; 45: 1043–1045.
18. McBurney JW, Teiken PJ, Moon MR. Propofol for treating status epilepticus. *Journal of Epilepsy* 1994; 7: 21–22.
19. Simpson KH, Halsall PJ, Curr CME, Stewart KG. Propofol reduces seizure duration in patients having anaesthesia for electroconvulsive therapy. *British Journal of Anaesthesia* 1988; 61: 343–344.
20. Modica PA, Templehoff R, White PF. Pro- and anticonvulsant effects of anesthetics (Part II). *Anesthesia and Analgesia* 1990; 70: 433–444.
21. Protocols for surgery of epilepsy in different centers. In: Loders HO, ed. *Epilepsy*. New York: Raven Press, 1992; 781–818.
22. Smith M. Anaesthesia for epilepsy and stereotactic surgery. In: Walters JM, Ingram GS, Jenkinson, eds. *Anaesthesia and Intensive Care for the Neurosurgical Patient*. London: Blackwell Scientific Publications, 1994; 318–344.
23. Kraemer DL, Spencer DD. Anesthesia in epilepsy surgery. In: Engel J, ed. *Surgical Treatment of the Epilepsies*. New York: Raven Press Ltd, 1993; 527–538.
24. Kofke WA, Snider MT, Young RSK, Ramer JC. Prolonged low flow isoflurane anesthesia for status epilepticus. *Anesthesiology* 1985; 62: 653–656.
25. Van Wieringen A. Effects of antiepileptic drugs on the electroencephalogram background and epileptiform activity. In: Wada JA, Ellingson RJ, eds. *Clinical Neurophysiology of Epilepsy*, EEG Handbook (*rev series, vol 4*), New York: Elsevier, 1990; 433–456.
26. Silbergeld DL, Mueller WM, Colley PS, Ojermann GA, Lettich E. Use of propofol (Diprivan) for awake craniotomies; technical note. *Surgical Neurology* 1992; 38: 271–272.

British Journal of Anaesthesia 1996; **76**: 503–507

Periodic cardiovascular and ventilatory activity during midazolam sedation

D. C. GALLETLY, T. B. WILLIAMS AND B. J. ROBINSON

Summary

We have examined the effects of sedation with midazolam 0.1 mg kg^{-1} and reversal with flumazenil 0.5 mg on beat-to-beat heart rate (HR) variability (HRV), systolic arterial pressure (SAP), finger photoplethysmograph amplitude (PLA) and impedence pneumography in eight volunteers. With the onset of sedation there was a small decrease in SAP and increase in HR (ns). Spectral analysis of the HR time series showed reductions in the proportion of power in the high (> 0.15 Hz) frequency "ventilatory" band consistent with midazolam causing vagolysis. During sedation, low frequency (< 0.05 Hz) oscillations of PLA, HR, SAP and ventilation were observed. These were thought to be secondary to activity of coupled cardiorespiratory neurones within the brain stem and the ventilatory periodicity appeared similar to that observed during the early stages of sleep. The diminished high frequency and increased low frequency oscillations induced by midazolam sedation were reversed by administration of flumazenil. (*Br. J. Anaesth.* 1996; **76**: 503–507)

Key words

Hypnotics benzodiazepine, midazolam. Antagonists benzodiazepine, flumazenil. Heart, heart rate. Arterial pressure, drug effects. Measurement techniques, plethysmography.

Analysis of heart rate variability (HRV) is a useful tool for examination of cardiac autonomic tone [1]. Because vagal and sympathetic components of the heart rate (HR) control mechanism are active over different frequency ranges, breakdown of a HR time series using Fourier methods of spectral analysis allows the shifting balance of autonomic control to be examined non-invasively. Similar analysis of systolic arterial pressure (SAP) variability allows extension of these observations to involvement of peripheral cardiovascular mechanisms [2]. Spectral methods of HR [3], SAP [2] and photoplethysmograph pulse amplitude [4] variability analysis have been used to examine the cardiovascular effects of i.v., volatile and inhalation anaesthesia.

Using statistical or time domain methods, the benzodiazepines were one of the first groups of drugs to be studied with regard to HRV; they were observed to cause a decrease in respiratory sinus arrhythmia [5]. Midazolam has modest but clinically important cardiovascular effects and its ability to obtund sympathetic and baroreflex function has been examined in detail [6]. In this study we have examined the effects of midazolam sedation on HRV, arterial pressure and plethysmograph amplitude.

Subjects and methods

After obtaining Ethics Committee approval and informed consent, we studied eight healthy male volunteers, mean age 32 (26–38) yr, mean weight 74 (64–82) kg. Studies were conducted between 08:00 and 11:00 with subjects fasted and refraining from caffeine-containing beverages for at least 12 h. Each subject lay supine and breathed oxygen 5 litre min^{-1} from a Hudson mask. A 22-gauge cannula was inserted into the right antecubital fossa. The following monitoring was commenced: HR (ECG lead CM_5, Corometrics Neo-Trak 502), SAP (continuous non-invasive arterial tonometry, Nellcor N-CAT 500), ventilation (impedance pneumograph, Corometrics Neo-Trak 502) and infra-red finger plethysmography (Hewlett–Packard 78330A). The ECG signal was interfaced with a purpose-built R wave detector generating a 50-ms pulse synchronous with each R wave peak. This pulse triggered a Macintosh IIcx computer with 16-bit ADC board (National Instruments) to record the R–R interval, respiratory amplitude and to determine the trough (diastole) and peak (systole) of each subsequent photoplethysmograph and arterial pressure wave. For graphical display purposes, the output from the impedence pneumograph is shown as the unsigned value through which a five-point moving averager has been passed.

In order to ensure that the ventilatory peak of HRV would not interfere with those frequencies less than 0.15 Hz, subjects were instructed to breathe in time with a 0.24-Hz microcomputer-generated auditory pulse throughout the study. After a 15-min stabilization period, the N-Cat 500 tonometer was calibrated and beat-to-beat recording of cardiorespiratory data commenced. After 5 min the tonometer was recalibrated and subjects received midazolam 0.1 mg kg^{-1} i.v. Twelve to fifteen minutes later the tonometer was recalibrated and flumazenil

---

D. C. GALLETLY, FANZCA, FRCA, T. B. WILLIAMS, BM, CHB, BMEDSC, B. J. ROBINSON, MSC, PHD, Section of Anaesthesia, Wellington School of Medicine, PO Box 7343, Wellington South, New Zealand. Accepted for publication: November 8, 1995.

Correspondence to D.C.G.

0.5 mg was administered i.v. Recordings were continued for a further 5-min period after administration of flumazenil.

A 5-min epoch of data was obtained towards the end of the control, midazolam and post-flumazenil periods. Fast Fourier analysis on 256-s segments of HR, respiration, SAP and plethysmograph amplitude (PLA) were performed as described previously [7]. Spectral power (area under the power spectrum curve) was calculated for each variable, for each period, in each subject. This was done for total power and for the power in four frequency bands: very low frequency 0.01–0.02 Hz; low frequency ("vasomotor") 0.02–0.08 Hz; mid frequency ("baroreflex") 0.08–0.15 Hz; and high frequency ("ventilatory") 0.15–0.45 Hz. The power in each band was then expressed as a percentage of the total for the corresponding subject and condition. In the time domain we calculated, for each subject and condition, the mean (SD) of each variable and for the R–R time series, the mean of the consecutive differences of the R–R interval time series.

Changes in the time domain measures and the proportion of power in each spectral range were analysed using ANOVA followed by paired *t* tests (Statview). Total spectral power in each frequency range were compared using the non-parametric Mann–Whitney *U* test.

Results

Table 1 shows the changes in time domain and spectral measures during the study period. The representative raw data are shown in figures 1 and 2.

After midazolam, there was a trend towards increasing HR ($P = 0.08$), decreasing SAP ($P = 0.08$) and increasing PLA. These changes differed between subjects and a clear, sustained, increase in HR, reversed by flumazenil, is apparent in figures 1 and 2. Sustained increases in PLA are shown in figure 2, but these changes appeared not to be reversed by flumazenil.

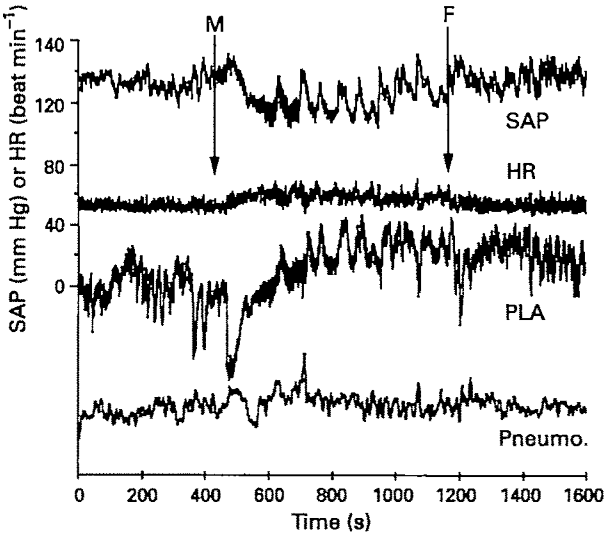


Figure 1 Effect of midazolam (M) and flumazenil (F) reversal of heart rate (HR), systolic arterial pressure (SAP), plethysmograph amplitude (PLA) and pneumogram amplitude (Pneumo.). PLA and pneumogram amplitude are shown on arbitrary scales.

Pneumogram amplitude during midazolam sedation was similar to the control, although during sedation the frequency of ventilation was observed to

Table 1 Effect of midazolam sedation and flumazenil reversal on time and frequency domain measures (mean (SD)). Con Diff RR = mean of the consecutive differences, irrespective of sign, between R–R intervals within the time series. Total spectral power is given in arbitrary units

	Control	Midazolam	*P*	Flumazenil	*P*
R–R interval					
Mean	992 (50)	880 (38.9)	ns	1010 (53.4)	ns
SD (within subject)	61.7 (3.7)	58.3 (7.8)	ns	56.7 (8.3)	ns
Mean Con Diff RR	45.3 (5.6)	29.3 (6.36)	ns	49.1 (10.5)	ns
Total power	1.73 (0.11)	1.47 (0.41)	ns	1.88 (0.54)	ns
% High	47.1 (6.3)	24.6 (6.5)	0.03	51.8 (6.0)	ns
% Mid	22.3 (3.6)	17.8 (3.0)	ns	13.7 (1.9)	0.05
% Low	24.4 (11.2)	35.8 (7.4)	ns	25.6 (4.7)	ns
% Very low	6.1 (1.6)	21.9 (4.1)	0.004	8.81 (2.0)	ns
Pneumograph amplitude					
Total power	766 (260)	410 (126)	ns	564 (246)	ns
Peak (Hz)	0.24 (0.0007)	0.26 (0.02)	ns	0.24 (0.004)	ns
SAP					
Mean	132.7 (5.9)	122.7 (4.8)	ns	124 (4.7)	ns
SD (within subject)	4.36 (0.78)	5.7 (0.63)	ns	4.22 (0.63)	ns
Total power	11.1 (5.4)	15.1 (5.3)	ns	9.3 (3.6)	ns
% High	15.3 (2.4)	17.3 (3.2)	ns	26.9 (4.1)	0.03
% Mid	11.9 (2.9)	11.4 (3.3)	ns	8.86 (1.5)	ns
% Low	47.4 (2.5)	45 (4.9)	ns	44.6 (5.8)	ns
% Very low	25.3 (2.6)	26.3 (6.4)	ns	19.6 (2.9)	ns
PLA					
Mean	6004 (1316)	7575 (606)	ns	8048 (495)	ns
SD (within subject)	471 (94.3)	990 (247)	ns	839 (223)	ns
Total power	115 (37)	416 (171)	0.03	300 (146)	ns
% High	28 (5.7)	12.7 (4)	0.05	27.4 (6.9)	ns
% Mid	10.7 (1.6)	6.3 (2)	ns	7.6 (2.2)	ns
% Low	40.0 (5.6)	53.0 (2.48)	0.05	42.2 (6.82)	ns
% Very low	21.3 (4)	27.9 (4.8)	ns	22.8 (7.2)	ns

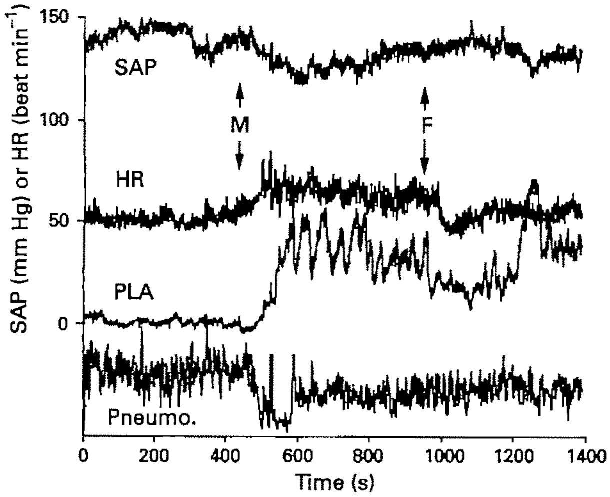


Figure 2 Effect of midazolam (M) and flumazenil (F) reversal of heart rate (HR), systolic arterial pressure (SAP), plethysmograph amplitude (PLA) and pneumogram amplitude (Pneumo.). PLA and pneumogram amplitude are shown on arbitrary scales.

increase slightly from the control value of 0.24 Hz to 0.26 (0.02) Hz. Time domain measures (SD, mean consecutive differences) of HR and SAP variability did not differ significantly from control values.

Spectral analysis revealed significant shifts in the HR and PLA power spectra. HR high frequency absolute power and the proportion of power in the high frequency band were reduced while the proportion of power in the band 0.01–0.02 Hz increased from 6 to 22%.

Examination of individual cardiorespiratory time series showed remarkable variability and complexity of effect. Consistent with the changes observed on spectral analysis, figures 1 and 2 show that with administration of midazolam, the appearance of very low and low frequency oscillations is evident in one or more of the cardiovascular measures (SAP, PLA, HR). These waves were most apparent in PLA and to the smallest extent in HR. The period of these oscillations was generally in the region of 40–75 s (0.013–0.025 Hz). The SAP waves appeared as transient elevations above a baseline level, rather than sinusoidal (figs 1, 2). The elevations were of two types: where SAP and PLA oscillations were out of phase, SAP elevations occurred during a reduction in plethysmograph amplitude; and where SAP and PLA oscillations were in phase, SAP pressure elevations were associated with an increase in plethysmograph amplitude (fig. 1).

Low frequency SAP and PLA fluctuations were not confined solely to the period of midazolam sedation but were present in at least one subject before drug administration. Indeed in this subject administration of midazolam caused a transient slowing or cessation of these waves for several minutes.

In three subjects oscillations in pneumogram amplitude were clearly observed in phase with the SAP waves; increased pneumogram amplitude occurred at the time of maximal increase in arterial pressure.

Discussion

The cardiovascular effects of midazolam have been investigated most frequently in patients with coronary artery disease [6, 8–11] and to a lesser extent in healthy subjects [12]. Midazolam causes a decrease in SAP, a small increase in HR, a reduction in cardiac output and little change or a decrease in systemic vascular resistance; ventricular filling pressures are usually decreased or may be unchanged and a direct cardiac depressant effect has been proposed. These haemodynamic changes most likely involve a reduction in SAP secondary to decreased systemic vascular resistance, decreased venous return caused by venodilatation and direct myocardial depression reducing cardiac output [13]. Small doses of diazepam have little effect on baroreflex function in patients with heart disease [14] whereas both diazepam 0.4 mg kg^{-1} and midazolam 0.3 mg kg^{-1}, when used for induction, cause significant but transient decreases in the pressor baroreflex slope which appears to be less than that induced by potent anaesthetic agents [6]. A compensatory, albeit blunted, baroreceptor-mediated increase in HR is therefore possible allowing haemodynamic status to be returned towards normal limits.

The respiratory effects of benzodiazepines are similarly modest but clinically important. Although having minimal effects on respiratory mechanics [15] they diminish central respiratory drive and the ventilatory response to inhaled carbon dioxide [16], and may induce both central apnoea and upper airway obstructive apnoea [17].

The autonomic circulatory and respiratory effects of benzodiazepines are largely mediated within the brain stem by modulation of GABAergic tone [18, 19]. GABA is involved in the endogenous regulation of SAP [20] and regulation of vagal outflow to the heart and respiratory tract [21]. Benzodiazepines are believed to attenuate vagal tone through a central parasympatholytic effect [5, 22–24]. The reduction in respiratory sinus arrhythmia (which is vagally mediated) by diazepam is believed to be mediated through the same mechanism. A vagolytic effect for midazolam can also be inferred both from its known ability to increase HR and the observed reduction in both absolute and proportional high frequency "ventilatory" beat-to-beat HRV in this study. HR periodicities within this frequency range (> 0.15 Hz) are mediated predominantly through fluctuations in vagal tone. Increased HR in concert with reduction in ventilatory induced HRV waves is seen after injection of midazolam.

An unexpected feature of midazolam sedation was the appearance of cardiovascular oscillations at frequencies < 0.025 Hz. Although these oscillations were most apparent in PLA and SAP they were also present in HR and in the pneumogram amplitude. The genesis of low frequency periodicities in HR at less than the Mayer wave or baroreflex frequency of approximately 0.1–0.15 Hz is generally ascribed to vasomotor fluctuations in peripheral vascular tone and indeed we observed them to be most apparent in the digital photoplethysmogram. These low frequency oscillations are well described in normal subjects [25, 26] and were clearly observed in one of our own subjects before sedation. We have observed [unpublished observations] similar fluctuations in unmedicated subjects who are warm and relaxed. Augmentation of these oscillations by ACE inhibitors suggests a modulatory role for the renin–angiotensin system [25] although some authors believe that they reflect an oscillation within a thermoregulatory reflex arc comprising peripheral thermoreceptors, afferent input, central integration and efferent sympathetic vascular response [27, 28]. It is of interest that some periodic SAP elevations were associated with a decrease in PLA while others were associated with an increase. The former probably reflect waves of sympathetic excitation which cause a secondary increase in arterial pressure while the latter may reflect a passive increase in PLA secondary to waves of SAP elevation, perhaps caused by constriction of other vasculature beds. Although these low frequency waves most likely represent sympathetic vasoconstriction, their appearance probably represents an overall decrease in peripheral cutaneous sympathetic tone from a relatively non-oscillatory tonic level at which vasoconstriction is more intense.

In several traces there was a clear association between respiratory activity and very low frequency oscillations in SAP and PLA; elevations in arterial pressure and decreased PLA occurring at the same time as increased ventilatory amplitude. Periodic ventilatory activity is well described in healthy adults under normal and hypoxic conditions, and in the elderly and neonates. In neonates, Waggener and colleagues observed periodic ventilatory patterns with short (approx. 20 s) and long (approx. 60 s) cycles [29]. In adults, Lenfant observed oscillations in healthy awake adults with periods of 2–6 breaths, 25–50 breaths and 150–200 breaths [30]. Ventilatory periodicity has been noted during sleep and is particularly marked during the early stages of sleep or sleep onset. It is possible that the ventilatory abnormalities of sleep apnoea may be an exaggerated form of this periodicity [31]. These ventilatory fluctuations may represent the activity of a Servo control loop oscillation in a chemoreceptor/ventilation arc, as postulated for the genesis of Cheyne–Stokes respiration. Indeed several theoretical and experimental studies having shown that prolonged circulatory times (e.g. heart failure) and enhanced chemoresponsiveness (e.g. altitude or hypoxic conditions) may lead to periodic patterns of breathing [32]. These mechanisms seem unlikely explanations for the observations in the present study however, as all subjects were healthy, the effects of midazolam on cardiac output are small and all subjects breathed oxygen which is a potent depressant of chemoreceptor activation. It seems probable that the slow periodic ventilatory effects were generated by a mechanism similar to that during light sleep and, as both cardiac and respiratory oscillations were coupled, they may have been generated within the interconnected respiratory and cardiovascular neurones of the brain stem [33]. Induction of these oscillations by midazolam and their reversal by flumazenil suggests they are mediated at least in part through brain stem GABAergic transmission. It is of interest that cardiovascular oscillations at these very low frequencies were seen far more commonly than ventilatory oscillations. This may indicate that cardiovascular oscillations within the brain stem are the primary source of ventilatory periodicity. The periodic ventilatory activity may be of clinical relevance to the observation of respiratory instability during benzodiazepine sedation and may warrant further study.

Administration of flumazenil to patients during benzodiazepine sedation results in few haemodynamic responses and minimal changes in SAP and HR [34]. Although these variables were changed little, administration of flumazenil was associated with return of periodic cardiorespiratory oscillations towards those before administration of midazolam.

In summary, we observed that midazolam caused changes in HR and HRV consistent with vagolysis, in some subjects provoked periodic (40–75 s) oscillations in HR, PLA and SBP and that these oscillations were at times coupled to periodic ventilatory activity. The study highlights the value of detailed time series analysis in demonstrating the significant effects of a drug on cardiorespiratory control when standard mean haemodynamic measures are changed little.

References

1. van Ravenswaaij-Arts C, Kollee L, Hopman J, Stoelinga G, van Geijn H. Heart rate variability. *Annals of Internal Medicine* 1993; **118**: 436–447.
2. Scheffer GJ, Ten Voorde BJ, Karemaker JM, Ros HH, De Lange JJ. Effects of thiopentone, etomidate and propofol on beat to beat cardiovascular signals in man. *Anaesthesia* 1993; **48**: 849–855.
3. Muzi M, Ebert TJ. Quantification of heart rate variability with power spectral analysis. *Current Opinion in Anesthesiology* 1993; **6**: 3–17.
4. Robinson B, Buyck HCE, Galletly DC. The effect of propofol anaesthesia on heart rate, arterial pressure and digital plethysmograph variability. *British Journal of Anaesthesia* 1994; 73: 167–173.
5. Adinoff B, Mefford I, Waxman R, Linnoila M. Vagal tone decreases following diazepam. *Psychiatry Research* 1992; **41**: 89–97.
6. Marty J, Gauzit R, Lefevre P, Couderc E, Farinotti R, Henzel C, Desmonts JM. Effects of diazepam and midazolam on baroreflex control of heart rate and on sympathetic activity in humans. *Anesthesia and Analgesia* 1986; **65**: 113–119.
7. Galletly DC, Tobin P, Robinson B, Corfiatis T. Effect of 30% nitrous oxide inhalation on spectral components of heart rate variability in conscious subjects. *Clinical Science* 1993; **85**: 389–392.
8. Samuelson PN, Reves JG, Kouchoukos NT, Smith LR, Dole KM. Hemodynamic responses to anesthetic induction with midazolam or diazepam in patients with ischemic heart disease. *Anesthesia and Analgesia* 1981; **60**: 802–809.
9. Reves JG, Samuelson PN, Lewis S. Midazolam induction in patients with ischaemic heart disease; haemodynamic observations. *Canadian Anaesthetists Society Journal* 1979; **26**: 402–409.
10. Schulte-Sasse U, Hess W, Tarnow J. Haemodynamic responses to induction of anaesthesia using midazolam in cardiac surgical patients. *British Journal of Anaesthesia* 1982; **54**: 1053–1057.
11. Marty J, Nitenberg A, Blanchet F, Zouioueche S, Desmonts JM. Effects of midazolam on the coronary circulation in patients with coronary artery disease. *Anesthesiology* 1986; **64**: 206–210.
12. Lebowitz P, Cote ME, Daniels AL, Ramsey FM, Martyn JA,

Teplick RS, Davison JK. Comparative cardiovascular effects of midazolam and thiopental in healthy patients. *Anesthesia and Analgesia* 1982; **61**: 771–775.

13. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. *Anesthesiology* 1985; **62**: 310–324.
14. Markievicz W, Hunt S, Harrison DC, Alderman EL. Circulatory effects of diazepam in heart disease. *Journal of Clinical Pharmacology* 1976; **16**: 637–644.
15. Southorn P, Rehder K, Didier E. Midazolam sedation and respiratory mechanics in man. *Anesthesiology* 1981; **55**: A367.
16. Forster A, Gardaz J, Suter PM, Gemperle M. Respiratory depression by midazolam and diazepam. *Anesthesiology* 1980; **53**: 494–497.
17. Montravers P, Dureuil B, Desmonts JM. Effects of i.v. midazolam on upper airway resistance. *British Journal of Anaesthesia* 1992; **68**: 27–31.
18. Taveira Da Silva AM, Pineo S, Gillis RA. Gamma-aminobutyric acid type A receptor blockade at the intermediate area of the ventral surface of the medulla counteracts the cardiorespiratory depression produced by intravenous midazolam. *Pharmacology* 1992; **45**: 154–161.
19. Gillis RA, Namath I, Easington C, Abrahams T, Guidotti A, Quest J, Hamosh P, Taveira Da Silva AM. Drug interaction with gamma amino butyric acid/benzodiazepine receptors at the ventral surface of the medulla results in pronounced changes in cardiorespiratory activity. *Journal of Pharmacology and Experimental Therapeutics* 1989; **248**: 863–870.
20. Suzuki M, Kuramochi T, Suga T. GABA receptor subtypes involved in the neuronal mechanisms of baroreceptor reflex in the nucleus tractus solitarii of rabbits. *Journal of the Autonomic Nervous System* 1993; **43**: 27–35.
21. Gillis RA, Quest JA, DiMicco JA. Central regulation of autonomic function by GABA receptors. In: Squires RF, ed. *GABA and Benzodiazepine Receptors*. Boca Raton, FL: CRC Press Inc, 1988: 141–147.
22. Haxhiu MA, Van Luteren E, Cherniack NS, Deal EC. Benzodiazepines acting on the ventral surface of medulla cause airway dilation. *American Journal of Physiology* 1989; **257**: R810–R815.
23. Hockman CH, Livingstone KE. Inhibition of reflex vagal bradycardia by diazepam. *Neuropharmacology* 1971; **10**: 307–314.
24. DiMicco JA. Evidence for control of cardiac vagal tone by benzodiazepine receptors. *Neuropharmacology* 1987; **26**: 553–559.
25. Akselrod S, Gordon D, Ubel F, Shannon D, Barger A, Cohen R. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat to beat cardiovascular control. *Science* 1981; **213**: 220–222.
26. Miyakawa K, Koepchen HP, Polosa C eds. *Mechanisms of Blood-Pressure Waves*. Berlin: Springer-Verlag, 1984.
27. Bini G, Hagbarth K, Hynninen P, Wallin B. Thermoregulatory and rhythm generating mechanisms governing the sudomotor and vasoconstrictor outflow in human cutaneous nerves. *Journal of Physiology (London)* 1980; **306**: 537–552.
28. Kitney R. An analysis of the nonlinear behaviour of the human thermal vasomotor control system. *Journal of Theoretical Biology* 1972 **52**: 231–248.
29. Waggener T, Stark A, Cohlan B, Frantz I. Oscillatory breathing patterns leading to apnoeic spells in infants. *Journal of Applied Physiology* 1982; **52**: 1288–1295.
30. Lenfant C. Time dependent variations of pulmonary gas exchange in normal man at rest. *Journal of Applied Physiology* 1967; **22**: 675–684.
31. Pack A, Silage D, Millman R, Knight H, Shore ET, Chung D. Spectral analysis of ventilation in elderly subjects awake and asleep. *Journal of Applied Physiology* 1988; **64**: 1257–1267.
32. Khoo M. Periodic breathing. In: Crystal R, West J, Barnes P, Cherniack N, Weibel E, eds. *The Lung: Scientific Foundations*. New York: Raven, 1990; 1419–1431.
33. Feldman JL, Ellenberger HH. Central co-ordination of respiratory and cardiovascular control in mammals. *Annual Review of Physiology* 1988; **50**: 593–606.
34. Marty J, Joyon D. Haemodynamic responses following reversal of benzodiazepine-induced anaesthesia or sedation with flumazenil. *European Journal of Anaesthesiology* 1988: (Suppl. 2): 167–171.

British Journal of Anaesthesia 1996; **76**: 508–510

Anatomical configuration of the spinal column in the supine position. III. Comparison of adolescent and adult volunteers

Y. HIRABAYASHI, R. SHIMIZU, K. SAITOH, H. FUKUDA, T. IGARASHI AND M. FURUSE

Summary

To clarify the anatomical configuration of the spinal column in the adolescent in the supine position, we have studied 10 adolescent (13–17 yr) and 10 adult (26–38 yr) volunteers using magnetic resonance imaging. T1-weighted sagittal midline magnetic resonance images of the spinal column were obtained with subjects in the supine position. The maximum angles of decline of the lumbar spinal canal did not differ between the adolescent (mean 13.6 (SD 3.3)°) and adult (12.4 (3.8)°) groups. The maximum angles of incline of the upper thoracic spinal canal were smaller in the adolescent group (15.9 (4.7)°) than in the adult group (26.4 (5.8)°). The median highest point of the lumbar spinal canal was located at L4 (range L3–4 to L4–5) in both groups. The lowest points of the thoracic spinal canal in the adolescent and adult groups were located at T8–9 (T7 to T9) and T8 (T6–7 to T9), respectively. This study showed that thoracic kyphotic curvature in adolescents was reduced significantly in the supine position compared with that in adults. This minimized thoracic kyphosis may explain, in part, the enhanced cephalad spread of subarachnoid hyperbaric anaesthetic solutions in adolescents. (*Br. J. Anaesth.* 1996; **76**: 508–510)

Key words

Anatomy, spinal column. Age factors. Adolescents. Anaesthetic technique, subarachnoid. Measurement techniques, nuclear magnetic resonance. Position, supine.

Hyperbaric anaesthetic solutions injected into the midlumbar subarachnoid space spread to higher levels in adolescents than in adults [1, 2]. However, the reason for this is not yet known. Hyperbaric anaesthetic solutions migrating cephalad in the supine position pool in the thoracic hollow [3, 4], and the anatomical configuration of the spinal column may influence the distribution of this pool [5].

With the advent of magnetic resonance (MR) imaging, the anatomical configuration of the spinal column in adults [6] and parturients [7] has been studied. However, data relating to adolescents have been lacking. The aim of this study was to assess the anatomical configuration of the spinal column in adolescents using MR imaging, compared with that in adults.

Subjects and methods

The Institutional Review Board approved our study and informed consent was obtained from all subjects or parents. We studied 10 adolescent (13–17 yr, five boys) and 10 adults (26–38 yr, five men) Japanese healthy volunteers. Subjects with back complaints were excluded. MR imaging examinations were performed with the subject in the supine position, with the legs extended horizontally and a headrest (1 cm in thickness) placed under the head on the MR platform. T1-weighted sagittal images of the cervical, thoracic and lumbar spine were obtained using an MR imaging system (MRT-200/FXIII super version, Toshiba Corporation, Tokyo, Japan) operating at 1.5 T with a single conventional surface coil. Technical specifications included a repetition time of 320–430 ms, an echo time of 15 ms, a slice thickness of 4 mm, a number of slices of 11 and a field of view of 30 cm. The sagittal midline images of the cervical, thoracic and lumbar spine were aligned to determine the following: maximum angle of decline of the lumbar spinal canal in the cephalad direction against the plane of the MR platform, maximum angle of incline of the upper thoracic spinal canal against the plane of the MR platform, the highest and lowest points of the spinal canal, and the levels of termination of the spinal cord and dural sac. The nearest vertebral body and intervertebral disc were used in determining the highest and lowest points (e.g. L1 indicated the body of the first lumbar vertebra; L1–2 showed the intervertebral disc between the first and second lumbar vertebrae).

The adolescent and adult groups were compared by Student's unpaired *t* test for parametric data and by the Mann–Whitney *U* test for non-parametric data. In addition, to assess differences between males and females, maximum angles of decline and incline of the spinal canal were compared by Student's unpaired *t* test. $P < 0.05$ was considered statistically significant.

Results

There were no differences between the adolescent and adult groups in height, weight or body mass index (table 1).

YOSHIHIRO HIRABAYASHI, MD, REIJU SHIMIZU, MD, KAZUHIKO SAITOH, MD, HIROKAZU FUKUDA, MD, TAKASHI IGARASHI, MD (Department of Anaesthesiology); MAKOTO FURUSE, MD (Department of Radiology); Jichi Medical School, Tochigi 329-04, Japan.
Accepted for publication: December 5, 1995.
Correspondence to Y.H.

Table 1 Mean (SD) [range] subject characteristics in the adolescent and adult groups. $^{***}P < 0.0001$

	Adolescent group	Adult group
Age (yr)	15 [13–17]***	31 [26–38]
Height (cm)	162 (7) [151–173]	164 (10) [142–178]
Weight (kg)	55 (11) [35–72]	60 (15) [37–85]
Body mass index ($kg\ m^{-2}$)	20.7 (3.1) [15.4–25.4]	22.2 (3.3) [17.4–27.8]

Table 2 Maximum angle of decline of the lumbar spinal canal (decline), maximum angle of incline of the upper thoracic spinal canal (incline), highest and lowest points of the spinal canal (high and low points), and levels of termination of the spinal cord and dural sac (spinal cord and dural sac) in the adolescent and adult groups (mean (SD) [range] or median (range)). $^{**}P < 0.001$

	Adolescent group	Adult group
Decline (°)	13.6 (3.3) [8–20]	12.4 (3.8) [8–20.5]
Incline (°)	15.9 (4.7)** [7.5–23]	26.4 (5.8) [18–36]
High point	L4 (L3–4 to L4–5)	L4 (L3–4 to L4–5)
Low point	T8–9 (T7 to T9)	T8 (T6–7 to T9)
Spinal cord	L1 (T12–L1 to L1)	L1 (T12–L1 to L1–2)
Dural sac	S2 (S2 to S2–3)	S2–3 (S2 to S3)

There was no difference between the adolescent and adult groups in the maximum angle of decline of the lumbar spinal canal. The maximum angle of incline of the upper thoracic spinal canal was smaller in the adolescent than in the adult group (table 2). There were no differences between the adolescent and adult groups in the highest and lowest points of the spinal canal or the levels of termination of the spinal cord and dural sac (table 2). There was no difference between males and females in the maximum angle of decline of the lumbar spinal canal (mean 11.7 (SD 2.4) (range 8–16)° *vs.* 14.3 (4.1) (8–20.5)°) or in the maximum angle of incline of the upper thoracic spinal canal (21.1 (7.4) (9–34.5)° *vs* 21.2 (8.0) (7.5–36)°). Figure 1 shows representative sagittal midline MR images of an adolescent girl and an adult woman.

Discussion

This study in healthy volunteers has demonstrated that thoracic kyphotic curvature in adolescents was reduced significantly in the supine position compared with that in adults.

In the adult in the standing position, it is widely accepted that the spinal column exhibits four curvatures in the sagittal plane: cervical—posterior concavity, thoracic—posterior convexity, lumbar—posterior concavity and sacral—posterior convexity [8]. Does the spinal column in the adolescent in the standing position exhibit the same four curvatures as in the adult? We cannot make definitive statements because no MR images in the standing position are available. What we can say, however, is that our study performed in the supine position demonstrated that the curvature of the spinal column in the adolescent differed significantly from that in the adult. The MR images from the adults verified the presence of the four curvatures in the supine position. In contrast, in the adolescents in the supine position, the thoracic kyphotic curvature was found to disappear substantially. Because the spinal column in the adolescent is expected to have a greater flexibility, it may become straight while the teenager is lying supine on a flat platform.

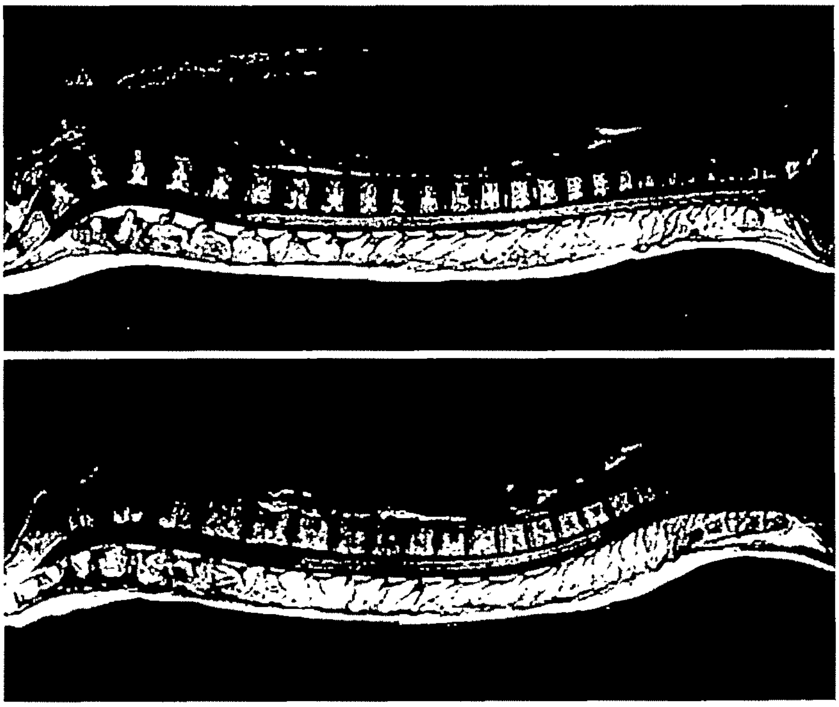


Figure 1 Sagittal midline MR images showing the spinal columns of a 13-yr-old girl (top) and a 31-yr-old woman (bottom). The spinal column in the adolescent becomes straight, particularly in the upper thoracic region, whereas that in the adult exhibits a typical thoracic kyphotic curvature.

When a patient is turned to the supine position after midlumbar subarachnoid injection of a hyperbaric solution, the solution spreads downwards from the injection site under the influence of gravity in both caudad and cephalad directions [3, 4]. The solution migrating to cephalad pools in the lowest region of the thoracic hollow and thus thoracic kyphotic curvature may affect the distribution of this pool [5]. Our study demonstrated that the adolescent has a minimized thoracic kyphotic curvature in the supine position. This minimal thoracic kyphosis may allow the drug to spread more easily to the higher thoracic segments. It has been found that hyperbaric amethocaine (tetracaine) [1] and cinchocaine (dibucaine) [2] injected into the midlumbar subarachnoid space spread to higher levels in adolescents than in adults. This suggests that the flatter thoracic curvature observed in supine adolescents is a likely reason for the higher levels of spinal anaesthesia with hyperbaric solutions in these teenagers.

Unlike hyperbaric anaesthetic solutions, isobaric anaesthetic solutions injected into the midlumbar subarachnoid space spread independently of the influence of gravity [9] and stay in the vicinity of the puncture site. In addition, hypobaric anaesthetic solutions tend to rise to the top of the lumbar lordotic curve [10]. Thoracic kyphotic curvature is therefore expected to have little effect on the spread of isobaric or hypobaric solutions. King and Wooten [11] compared spinal anaesthesia with isobaric amethocaine in adolescent and adult patients and found no difference in spread between the groups. The difference in thoracic kyphotic curvature between the adolescent and adult may not affect the spread of spinal anaesthesia with isobaric solutions.

In addition to the anatomical configuration of the spinal column, the level of termination of the spinal cord and volume of cerebrospinal fluid (CSF) is thought to influence the spread of anaesthetic solutions within the subarachnoid space in the adolescent [1]. It is well known that in young children the spinal cord is close to the sacral canal, and that as they grow, the end of the cord retracts cephalad relative to the spinal canal. In this study we failed to demonstrate any difference in the level of termination of the spinal cord between the adolescent and adult groups. The end of the spinal cord is expected to assume its adult position before 13–17 yr of age. In addition, our sagittal MR images provided no information on the volume of CSF below the termination of the spinal cord. Further studies, including quantitative axial MR images [12], are needed to clarify this issue.

This study was performed on subjects of Japanese origin. The results of this study can be applied directly only to people of the same race and within the age, height and weight range of the subjects in this study. Our volunteers were all of relatively small stature and weight compared with European or North American subjects. It is therefore possible that different results might be encountered in these populations.

Although in adolescents there is a very wide range of height and weight values compared with adult populations, we failed to demonstrate any differences between the two groups in height, weight or body mass index. This probably reflected a type 2 error, because the numbers studied were small. In addition, we failed to show any differences between males and females. However, the results of this study indicated a greater angle of decline in females, which is consistent with the larger buttocks of females. This difference was consistent with the results of our previous study [6]; however, it would be necessary to study a substantially larger population to confirm possible differences.

Acknowledgements

We thank Mr K. Saitoh and other members of the staff of the magnetic resonance imaging unit.

References

1. Hirabayashi Y, Shimizu R, Saitoh K, Fukuda H. Subarachnoid spread of hyperbaric amethocaine in adolescents. *British Journal of Anaesthesia* 1995; 74: 41–45.
2. Hirabayashi Y, Shimizu R. The spread of spinal anesthesia in young patients. *Masui (Japanese Journal of Anesthesiology)* 1993; 42: 1274–1277.
3. Kitahara T, Kuri S, Yoshida J. The spread of drugs for spinal anesthesia. *Anesthesiology* 1956; 17: 205–208.
4. Beardsley D, Holman S, Gantt R, Robinson RA, Lindsey J, Bazaral M, Stewart SFC, Stevens RA. Transient neurologic deficit after spinal anesthesia: local anesthetic maldistribution with pencil point needles? *Anesthesia and Analgesia* 1995; **81**: 314–320.
5. Greene NM. Distribution of local anesthetic solutions within the subarachnoid space. *Anesthesia and Analgesia* 1985; **64**: 715–730.
6. Hirabayashi Y, Shimizu R, Saitoh K, Fukuda H, Furuse M. Anatomical configuration of the spinal column in the supine position. I. A study using magnetic resonance imaging. *British Journal of Anaesthesia* 1995; 75: 3–5.
7. Hirabayashi Y, Shimizu R, Fukuda H, Saitoh K, Furuse M. Anatomical configuration of the spinal column in the supine position. II. Comparison of pregnant and non-pregnant women. *British Journal of Anaesthesia* 1995; 75: 6–8.
8. Moore KL. *Clinically Oriented Anatomy*, 3rd Edn. Baltimore: Williams & Wilkins, 1992; 326.
9. Wildsmith JAW. Baricity and spinal anesthesia: What solution when? *Anesthesiology Clinics of North America* 1992; 10: 31–43.
10. Southworth JL, Hingson RA, Pitkin WM. *Conduction Anesthesia*, 2nd Edn. Philadelphia: JB Lippincott, 1953; 13.
11. King HK, Wooten DJ. Subarachnoid spread of isobaric tetracaine in adolescents. *British Journal of Anaesthesia* 1994; 75: 245–246.
12. Westbrook JL, Renowden SA, Carrie LES. Study of the anatomy of the extradural region using magnetic resonance imaging. *British Journal of Anaesthesia* 1993; 71: 495–498.

British Journal of Anaesthesia 1996; **76**: 511–514

Convective warming combined with vasodilator therapy accelerates core rewarming after coronary artery bypass surgery

S. J. HARRISON AND J. PONTE

Summary

In a prospective, randomized, controlled study, we have investigated the effect of forced air warming on the rate of change of nasopharyngeal and rectal temperatures in 20 patients after coronary artery bypass grafting. All patients had nasopharyngeal temperatures less than 36 °C on arrival in the intensive care unit and received an infusion of glyceryl trinitrate 15 mg h^{-1}, but none received inotropes. Ten patients were warmed under an aluminized plastic "space" blanket (control group) and 10 were warmed under a "Bair Hugger" blanket connected to its power unit on "high" setting (Bair Hugger group). The rates of increase in nasopharyngeal temperature were 0.4 and 0.95 °C h^{-1}, respectively, in the control and Bair Hugger groups ($P < 0.01$) during the first 2 h after operation. Over the same period of time, rectal temperatures increased at a rate of 0.25 and 0.75 °C h^{-1} in the control and Bair Hugger groups, respectively ($P < 0.01$). (*Br. J. Anaesth.* 1996; **76**: 511–514)

Key words

Temperature, body. Temperature, monitoring. Surgery, cardiovascular. Equipment, blankets. Equipment, warming devices. Monitoring, temperature.

A decrease in body core temperature, termed "afterdrop", occurs frequently during the first 60–90 min of recovery after cardiac surgery; this is often the single factor for delaying return to spontaneous ventilation and tracheal extubation in this group of patients. Postoperative hypothermia may be attenuated by altering the management during cardiac surgery, such as adopting a "normothermic" technique during cardiopulmonary bypass, prolonging the rewarming period or infusing vasodilators while increasing pump flow [1, 2]. Often these measures are not successful and postoperative hypothermia occurs, especially if complications supervene (e.g. difficult haemostasis) which prolong the operative period after restoring normal circulation. Thus there is a clear need for a simple and effective tool to accelerate core rewarming during recovery.

Forced warm air devices are a proven, simple, safe and inexpensive means of preventing hypothermia during operation [3–5]. The available evidence that this type of warming device can be used to accelerate rewarming of core temperature after operation is controversial. In a recent study, Moors and colleagues [6] could not show that forced warm air, after coronary artery bypass surgery, accelerated the rate of increase in core temperature. In contrast, other authors found that in non-cardiac surgery, forced warm air was effective in rewarming the core of patients after operation [7]. We decided to perform this study to ascertain if the concomitant use of forced warm air and cutaneous vasodilatation is effective in accelerating core rewarming after coronary artery bypass surgery. Preliminary results have been published in abstract form [8].

Patients and methods

After obtaining hospital Ethics Committee approval and written informed consent, we studied 20 patients, allocated to two groups of 10 ("control" and "Bair Hugger") who were admitted for elective coronary artery bypass grafting and who had "good" left ventricular function (ejection fraction > 50 %). The general anaesthetic (based on propofol, fentanyl and vecuronium) and surgical techniques were similar for all patients. In each group, six patients had unilateral stripping of leg veins and subsequent wrapping of the leg with an elastic bandage. In four patients in each group, veins were not harvested for grafting, mammary arteries only were used for coronary bypass conduits. With the exception of one patient who was cooled to 28 °C, all other patients were cooled during cardiopulmonary bypass to nasopharyngeal temperatures of 30–32 °C and then rewarmed to 37.3–38.3 °C; bypass and cooling times were noted. After surgery, patients were transferred to the intensive care unit and included in the study only if their nasopharyngeal temperature was less than 36 °C on arrival and inotropic support was not required. Relevant data on the selected patients are shown in table 1; there were no significant differences between the two groups (overall ranges), using the unpaired *t* test or the Mann–Whitney *U* test, in bypass time (49–97 min), cooling time (24–61 min) and total operating time (3.5–5 h).

On arrival in the intensive care unit patients were randomized to receive either a "space" blanket (control group) or a Bair Hugger blanket (Actamed Ltd, Wakefield). In the control group an aluminized plastic "space" blanket (Universal Hospital Supplies Ltd, London) was placed above the sheet and beneath the conventional hospital blankets; in the

---

S. J. HARRISON, FRCA, J. PONTE, PHD, FRCA, Department of Anaesthetics, King's College Hospital, Denmark Hill, London SE5 9RS. Accepted for publication: November 11, 1995.

Correspondence to J.P.

Table 1 Patient data (mean (SD) or median (range)). Comparisons between the two groups showed $P > 0.05$ for all variables. NPT = Nasopharyngeal temperature

	Control ($n = 10$)	Bair Hugger ($n = 10$)
Age (yr)	60.5 (49–73)	64.3 (51–73)
Weight (kg)	83.6 (12.1)	74.7 (10.0)
Body mass index (kg m^{-2})	27.8 (4.0)	26.1 (2.7)
NPT on arrival at ICU (°C)	35.7 (35.3–35.9)	35.5 (34.7–35.8)
Ambient temperature (°C)	22.3 (0.9)	22.6 (0.8)

Bair Hugger group a whole body Bair Hugger blanket was placed on top of the patient next to the skin, beneath conventional hospital sheets and blankets, and connected to a Bair Hugger 275E power unit on "high" setting. In both groups the patient's head, and the hand and foot from which temperature measurements were being taken were left uncovered.

TEMPERATURE MEASUREMENTS

Baseline temperature readings of nasopharyngeal, rectal, fingertip and toe temperatures were obtained 10 min after arrival in the intensive care unit and at 15-min intervals thereafter. Nasopharyngeal and rectal temperatures were measured with Yellow Springs 400 series thermistor probes, displayed and stored on a Marquette Tramscope 12C monitor. Fingertip and toe skin temperatures were measured using Mallinkrodt insulated skin thermocouple probes connected to a Mallinkrodt Hi-Lo Temp model 8200 three-channel temperature monitor. The rates of temperature change during the first 2 h after operation were compared between control and Bair Hugger groups for all four measurement sites using the Mann–Whitmey U test. Differences in the number of patients achieving core temperatures greater than 37 °C at 2 h were compared using the chi-square test with Yates' correction. Ambient temperature and humidity were recorded for each patient by means of a Vaisala HMI31 monitor. Ambient temperature ranged between 20.8 and 23.3 °C and relative humidity between 21 % and 38.2 % for all patients, with no differences between the two groups.

POSTOPERATIVE MANAGEMENT

All patients received an infusion of glyceryl trinitrate at a minimum rate of 15 mg h^{-1}. Systolic arterial pressure was maintained at 90–130 mm Hg in all patients. This was attained either by an i.v. infusion of gelatin (or blood if haemoglobin was < 8 g dl^{-1}) when systolic arterial pressure approached 90 mm Hg, or by increasing the glyceryl trinitrate infusion when pressure approached 130 mm Hg. Boluses of hydralazine 10 mg i.v. were used occasionally if glyceryl trinitrate 30 mm h^{-1} was insufficient to maintain systolic arterial pressure at or below 130 mm Hg. All i.v. fluids were warmed to 36.5 °C in a water bath. Blood lost through pericardial and mediastinal drains into an autotransfusion reservoir was returned to the patient at room temperature at a maximum rate of 600 ml h^{-1}. Patients were sedated with an infusion of propofol 50–200 mg h^{-1} and their lungs ventilated mechanically during the period of measurements, maintaining Pa_{CO_2} at 4.5–5.5 kPa. The occurrence of shivering was noted and, if present, was suppressed promptly first by increasing the infusion of propofol and then using morphine boluses (2–5 mg i.v.) supplemented with vecuronium boluses (2–4 mg i.v.) if morphine was ineffective. The incidence of shivering was compared between control and Bair Hugger using the chi-square test with Yates' correction.

Results

The rate of postoperative increase in temperature during the first 2 h was greater in the Bair Hugger

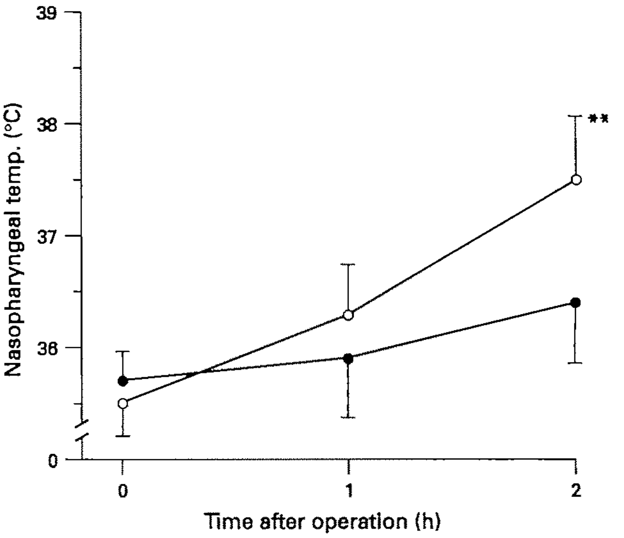


Figure 1 Mean (SD) nasopharyngeal temperature on arrival in the intensive care unit (0), and at 1 and 2 h after operation, in two groups of 10 patients each, after cardiac surgery. Patients in the control group (●) were managed with conventional blankets and an aluminium foil blanket, while those in the Bair Hugger group (○) were managed with a forced warm air device. Temperatures were significantly higher in the Bair Hugger group 2 h after operation. (** $P < 0.01$).

Table 2 Median (range) rate of increase in temperature (°C h^{-1}) during the first 2 h after operation at the four measuring sites in the two groups of patients. The Mann–Whitmey U test was used to compare the two groups

	Control ($n = 10$)	Bair Hugger ($n = 10$)	P
Nasopharyngeal	0.40 (0–0.75)	0.95 (0.70–1.15)	< 0.01
Rectal	0.25 (0–0.65)	0.75 (0.45–1.20)	< 0.01
Toe	−1.15 (−4.00 to 0.05)	0.75 (−0.55 to 4.90)	< 0.01
Fingertip	−2.25 (−4.35 to −0.20)	1.30 (−1.45 to 2.75)	< 0.01

group compared with the control group ($P < 0.01$) at all recorded sites (table 2). Patients in the Bair Hugger group often reached a nasopharyngeal temperature in excess of 37 °C at 2 h, thus forcing the end of the warming intervention. Although measurements were obtained during the first 4 h after operation in all patients, it was decided to confine the study period for the purpose of comparisons to the first 2 h after operation.

At the end of the second hour after operation, one patient in the control group and nine patients in the Bair Hugger group had reached a nasopharyngeal temperature of 37 °C or higher ($P < 0.01$) (fig. 1). Shivering was noted in five patients in the control group and in three patients in the Bair Hugger group but this difference was not significant. In the control group five patients were given morphine boluses, three were given hydralazine and another three vecuronium to suppress shivering. In the Bair Hugger group three patients were given morphine, one was given hydralazine and none needed vecuronium to suppress shivering.

Discussion

In contrast with a recent study in a similar group of patients [6], our results demonstrated that forced warm air, using a Bair Hugger system, accelerated the rate of warming not only of skin but also of nasopharyngeal and rectal temperatures in patients after coronary artery surgery with hypothermic bypass. This discrepancy may be explained by differences in study design; for example, the routine use of high doses of glyceryl trinitrate after operation in our patients may have caused cutaneous vasodilatation, modifying the exchange of heat between the warming device and the patient. It is also possible that the doses of glyceryl trinitrate used in our study accelerated cutaneous heat loss in the patients in the control group. This, however, seems unlikely as patients in this group did eventually warm up, despite the absence of shivering, at a rate close to that usually observed in the absence of glyceryl trinitrate.

Studies of heat transfer through the skin into the body are scarce. There are reports in awake normal subjects managed with surface warming devices [9] but none in unconscious patients undergoing ventilation. Our results should be regarded as preliminary in this respect; they indirectly suggest that heat transfer from the warming device into the patient is possible, compared with merely preventing heat loss. The rate of increase of temperature in the four measured sites is not easily accounted for by the physiological non-shivering thermogenesis expected in postoperative, sedated patients. In awake, normal, non-shivering subjects, metabolism generates approximately 100 W of which approximately 10 W is lost through breathing and 90 W through the skin. If skin loss could be abolished, one would expect mean body temperature to increase initially at a rate of 1 °C h^{-1}, assuming a specific heat of approximately 0.83 kCal kg^{-1} $°C^{-1}$ for the whole body. In sedated patients undergoing ventilation, metabolism is reduced and the rate of increase in mean body temperature during zero skin heat loss should be somewhat less than 1 °C h^{-1}. Although we did not monitor sufficient sites to compute mean body temperature changes, the rate of increase at all four sites measured was > 0.75 °C h^{-1} in the Bair Hugger group. This suggests that the Bair Hugger treated patients at least achieved zero heat loss through the skin, if not actual heat gain from the warming device. Ideally, we should have monitored temperature at another six sites to estimate mean body temperature and used indirect calorimetry during the rewarming period to calculate metabolic rate. This would have allowed calculation of the expected mean body temperature increase per hour as a function of the heat generated by metabolism and a comparison with the measured changes, from which it could be calculated whether heat gain in excess of metabolism was present. Thus, for a direct demonstration of heat transfer from the warming device to the patient, a differently designed study is needed. Heat flow probes strategically placed over the skin would also be necessary for such a study [9].

The discrepancy between our results and those of Moors and colleagues [6] in which it was suggested that forced air warming devices can only expand the volume of the body "core" rather than increase its temperature, may be explained by differences in study design other than the postoperative use of vasodilators not used routinely by these authors. The use of inotropes was not stated and, more importantly, the management of shivering was not addressed. In our view, studies failing to accurately report the use of inotropes during recovery should be interpreted with caution because of the well known thermogenic effects of catecholamines [10, 11]. We were meticulous in our efforts to promptly abolish shivering in our patients because of its contribution to total body heat generation. For this purpose morphine was used [12] and, if necessary, vecuronium, in addition to a routine background sedative dose of propofol. Such manoeuvres attenuated the physiological responses to hypothermia other than shivering [13] allowing for a clearer comparison of the effects of the warming strategy between the two groups of patients. Although the difference was not significant, five patients shivered in the control group compared with three in the Bair Hugger group. Had we not abolished shivering, we would have expected acceleration of the rate of warming in the shivering patients which might have blurred the difference between the two groups. To enhance further the expected difference between the two groups, the "high" setting (43 °C) on the Bair Hugger power unit was used routinely, as reported previously by others [3, 4].

Perioperative hypothermia remains a common problem in cardiac surgery and is associated with increased plasma catecholamine concentrations and an increase in metabolic rate (shivering), causing increased cardiovascular morbidity [14]. Our findings appear to illustrate the stressful effects of postoperative hypothermia: for example, more patients needed hydralazine, morphine and vecuronium in the control than in the Bair Hugger group. Although these differences did not reach significance we suspect that this was because of the small number of patients studied.

The recent trend towards a shorter postoperative period of mechanical ventilation and early extubation has highlighted the need for prevention and treatment of hypothermia. Despite careful temperature management during bypass, a proportion of patients is hypothermic at the end of surgery. The management of this condition has been based traditionally on preventing further heat losses by nursing the patient in a warm environment and covering the skin with thermal insulation devices such as aluminium foil. Despite these measures, core temperature often decreases further during the first hour after operation, as indeed we observed in several of our patients in the control group. Such "after-drop" in core temperature is possibly related to the redistribution of heat from the core to other body compartments, especially skeletal muscle [15]. Other types of heating devices have been tried in this setting; the oesophageal heat exchanger, for example, has been shown to be ineffective and radiant heaters to be effective only in warming the skin but at the expense of convenience [16].

References

1. Noback CR, Tinker JH. Hypothermia after cardiopulmonary bypass in man: Amelioration by nitroprusside induced vasodilation during rewarming. *Anesthesiology* 1980; **53**: 277–280.
2. Joachimsson P-O, Nyström S-O, Tydén H. Postoperative ventilatory and circulatory effects of extended rewarming during cardiopulmonary bypass. *Canadian Journal of Anaesthesia* 1989; **36**: 9–19.
3. Müller CM, Langenecker S, Andel H, Nautschev I, Holtzenbein TJ, Zimpfer M. Forced-air warming maintains normothermia during orthotropic liver transplantation. *Anaesthesia* 1995; **50**: 229–232.
4. Bennett J, Ramachandra V, Webster J, Carli F. Prevention of hypothermia during hip surgery: effect of passive compared with active skin surface warming. *British Journal of Anaesthesia* 1994; **73**: 180–183.
5. Russell SH, Freeman JW. Prevention of hypothermia during orthotopic liver transplantation: comparison of three different intraoperative warming methods. *British Journal of Anaesthesia* 1995; **74**: 415–418.
6. Moors AH, Pickett JA, Woolman PS, Bethune DW, Duthie DJR. Convective warming after hypothermic cardiopulmonary bypass. *British Journal of Anaesthesia* 1994; **73**: 782–785.
7. Lennon RL, Hosking MP, Conover MA, Perkins WJ. Evaluation of a forced-air system for warming hypothermic postoperative patients. *Anesthesia and Analgesia* 1990; **70**: 424–427.
8. Harrison S, Ponte J. Convective warming combined with vasodilator therapy accelerates rewarming following cardiac surgery. *British Journal of Anaesthesia* 1995; **75**:659P.
9. Sessler DI, Moayeri BA. Skin surface warming: heat flux and central temperature. *Anesthesiology* 1990; **73**: 218–224.
10. Fellows IW, Bennett T, MacDonald IA. The effect of adrenaline upon cardiovascular and metabolic functions in man. *Clinical Science* 1985; **69**: 215–222.
11. Amoroso P, Wilson SR, Moxham J, Ponte J. Acute effects of inhaled salbutamol on the metabolic rate of normal subjects. *Thorax* 1993; **48**: 882–885.
12. Rodriguez JL, Weissman C, Damask MC, Askanasi J, Hyman AI, Kinney JM. Morphine and postoperative rewarming in critically ill patients. *Circulation* 1983; **68**: 1238–1246.
13. Matsukawa T, Kurz A, Sessler DI, Bjorksten AR, Merrifield B, Cheng C. Propofol linearly reduces the vasoconstriction and shivering thresholds. *Anesthesiology* 1995; **82**: 1169–1180.
14. Frank SM, Higgins MS, Breslow MJ, Fleisher LA, Gorman RB, Sitzmann JV, Raff H, Beattie C. The catecholamine, cortisol and hemodynamic responses to mild perioperative hypothermia. *Anesthesiology* 1995; **82**: 83–93.
15. Davis FM, Parimelazhagan KN, Harris EA. Thermal balance during cardiopulmonary bypass with moderate hypothermia in man. *British Journal of Anaesthesia* 1977; **49**: 1127–1132.
16. Imrie MM, Ward M, Hall GM. A comparison of patient rewarming devices after cardiac surgery. *Anaesthesia* 1991; **46**: 44–48.

British Journal of Anaesthesia 1996; **76**: 515–518

Single-dose i.v. granisetron in the prevention of postoperative nausea and vomiting

A. J. WILSON, P. DIEMUNSCH, B. G. LINDEQUE, H. SCHEININ, H. S. HELBO-HANSEN, M. V. A. M. KROEKS AND K. L. KONG

Summary

In this randomized, double-blind, parallel group, placebo-controlled, dose-ranging study, we have compared three doses (0.1 mg, 1.0 mg and 3.0 mg) of the 5-HT$_3$ receptor antagonist, granisetron (Kytril), as prophylactic therapy for the prevention of postoperative nausea and vomiting. The aims were to determine the optimal dose of granisetron and to evaluate its safety profile. We studied 527 adult patients, undergoing elective open abdominal surgery or vaginal hysterectomy during general anaesthesia. Antiemetic prophylaxis with a single dose of granisetron 1.0 mg or 3.0 mg resulted in a significant reduction ($P < 0.001$ compared with placebo) in the numbers of patients experiencing postoperative vomiting, or nausea, or who achieved total control during the postoperative periods 0–6 h and 0–24 h. The two higher doses of granisetron (1.0 mg and 3.0 mg) provided effective prophylaxis against vomiting, with 78% and 77% of patients, respectively, being free from vomiting in the first 6 h after surgery, and 63% and 62% in the first 24 h. This compares with 50% and 34% at 0–6 h and 0–24 h, respectively, in the placebo group. Granisetron was well tolerated and the optimum dose was 1.0 mg (*Br. J. Anaesth.* 1996; **76**: 515–518)

Key words
Vomiting, nausea. Vomiting, antiemetics.

Granisetron (Kytril) is a highly selective and potent 5-HT$_3$ receptor antagonist [1]. It is believed to act specifically at 5-HT$_3$ receptors on the vagal afferent nerves of the gut. Studies have shown that granisetron (in contrast with ondansetron) produces irreversible block of the 5-HT$_3$ receptor [2, 3] which may account for the long duration of action of the drug. Furthermore, in studies comparing the potency of three different 5-HT$_3$ receptor antagonists, granisetron was shown to have a greater potency than tropisetron, which in turn had a greater potency than ondansetron [4]. Granisetron has proved to be safe and effective against nausea and vomiting induced by cancer chemotherapy when given as a single 3.0 mg dose [5]. Therefore, in this study we have determined the optimal dose of granisetron (0.1, 1.0 or 3.0 mg), given as a single i.v. injection for prevention of postoperative nausea and vomiting (PONV), and evaluated the safety profile of granisetron when given before surgery.

Patients and methods

This multinational, multicentre study was carried out in 35 centres in Denmark, Finland, France, Italy, The Netherlands, South Africa, Switzerland and the UK with the approval of the Ethics Committees in each centre. It was a randomized, double-blind, parallel group, dose-ranging study comparing three single doses of i.v. granisetron with placebo.

We studied patients of both sexes, over the legal age of consent, who were undergoing elective open cholecystectomy, open gynaecological procedures or vaginal hysterectomy during general anaesthesia. Exclusion criteria were ASA class IV or V, body weight 25% or more above ideal, breast feeding or pregnancy, known sensitivity to 5-HT$_3$ antagonists or if patients were already experiencing vomiting or moderate-to-severe nausea or had taken antiemetic drugs in the 24 h before surgery.

A history of susceptibility to motion sickness or past history of PONV was recorded. Among female patients, a menstrual history was also obtained, as the incidence of PONV is known to be affected by the phase of the menstrual cycle [6].

After giving written informed consent, patients were allocated to a treatment group to receive one of the three doses of granisetron or placebo using a computer-generated randomization schedule. Granisetron or placebo was given as an i.v. injection over 30 s, 5 min before induction of anaesthesia. The study was blinded by each syringe being preloaded with the same amount of fluid but a different dose of granisetron (0, 0.1 mg, 1.0 mg or 3.0 mg), depending

---

A. J. WILSON, MB, CHB FFARCSI, City Hospital, Dudley Road, Birmingham, UK. P. DIEMUNSCH, MD, CESAR, Hospices Civils de Strasbourg, Strasbourg, France. B. G. LINDEQUE, MD, FCOG(SA), Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Pretoria, Pretoria, South Africa. H. SCHEININ, MD, Department of Anaesthesiology, Turku University Central Hospital, Turku, Finland. H. S. HELBO-HANSEN, MD, Odense University Hospital, Odense, Denmark. M. V. A. M. KROEKS, MD, PHD, Department of Gynaecology and Obstetrics, Diakonessenhuis, Utrecht, The Netherlands. K. L. KONG, MD, FRCA, City Hospital, Dudley Road, Birmingham, UK. Accepted for publication: November 11, 1995.

Correspondence to K.L.K.

on the randomization code. Patients were scheduled to receive general anaesthesia with the following agents: no premedication or benzodiazepine premedication, i.v. barbiturate induction, maintenance with nitrous oxide and a volatile agent in oxygen, intraoperative opioid analgesics, neuromuscular block and antagonism of neuromuscular block as required, and postoperative analgesia with opioid or non-opioid analgesics, or both. Duration of operation and the time taken for patients to respond to verbal commands (recovery time) were also noted.

Patients were assessed by the investigators 1, 2, 6 and 24 h after operation. At each of these times, the incidence of nausea, vomiting, or both, and the patient's subjective assessment of pain were recorded. The time of onset of the first episode of nausea, vomiting, or both, was also noted. The major measures of efficacy were number of patients who did not report any nausea or vomiting 0–6 h and 0–24 h after recovery from anaesthesia. Patients who experienced nausea or vomiting, or both, such that further antiemetic treatment was deemed necessary by the attendant physician, were given rescue antiemetics (either prochlorperazine or metoclopramide) and classed as treatment failures. A patient with total control was defined as one who had no nausea, no vomiting, no rescue therapy and had not been withdrawn during the 24 h after anaesthesia.

Patients were followed up from 4 to 8 days after operation. Return of bowel function was assessed after 6 h and 24 h by recording the return of flatulence or evacuation of stool. Vital signs (heart rate, arterial pressure and temperature) were recorded. Blood samples were obtained before drug administration, at 24 h and at follow-up, for plasma creatinine, alkaline phosphatase and alanine aminotransferase concentrations, haemoglobin content, red blood cells, packed cell volume, white blood cells and platelet count.

The occurrence of adverse events during the study was monitored. For any event, the following details were recorded: time it started and stopped, or whether or not it was continuous; course; intensity; suspected relationship to study treatment; and whether or not corrective therapy was given.

Our aim was to recruit at least 480 patients into the study, with approximately 120 patients in each treatment group. This was the number needed in order to detect a 22% difference between active groups and placebo (90% power) assuming a "no vomiting" rate of 50% (based on previous observations of placebo no vomiting rates [6, 7]).

STATISTICAL ANALYSIS

The chi-square test was used to detect differences between treatment groups for "no vomiting", "no nausea", total control and adverse events. The Cox log rank test was used to detect differences between treatment groups in the survival distributions of the variables: time to less than total control, time to first episode of vomiting, time to first episode of nausea and time to first use of rescue antiemetics over the first 24 h. Pairwise comparisons were made between placebo and each of the granisetron treatment groups using the modified Bonferroni correction to maintain an overall significance level of 5%. Logistic regression analysis (at a significance level of 10%) was used to investigate the presence of any treatment-by-factor interaction.

Results

A total of 527 patients (96% women) were recruited and allocated randomly to receive placebo ($n = 133$), granisetron 0.1 mg ($n = 132$), granisetron 1.0 mg ($n = 134$) or granisetron 3.0 mg ($n = 128$). There were no significant differences in patient characteristics between the four groups (table 1).

The groups were comparable in the type of surgery performed, anaesthetic agents and technique used, duration of operation and perioperative use of opioid analgesics (table 2).

The two larger doses of granisetron (1.0 mg and 3.0 mg) provided effective prophylaxis against vomiting: 63.4% and 61.7% of patients, respectively, were free from vomiting in the first 24 h after surgery ($P < 0.001$ *vs* placebo), and 78.4% and 76.6%, respectively, in the first 6 h ($P < 0.001$ *vs* placebo). The results are summarized in table 3.

Significantly more patients did not require rescue antiemetics (prochlorperazine or metoclopramide) in the granisetron 1.0 mg ($P = 0.007$) and granisetron 3.0 mg ($P = 0.003$) groups than in the placebo group. Overall, the distribution of survival times to first episode of vomiting, first episode of nausea, less than total control and first use of rescue antiemetic therapy differed significantly ($P < 0.01$) between the granisetron 1.0 mg and 3.0 mg groups and the placebo group, with the granisetron groups performing better.

There were no significant treatment-by-factor interactions for age, weight, previous history of PONV–motion sickness, menopausal status, duration of anaesthesia or study country (table 4). Only two significant treatment-by-factor interactions emerged from the analysis: type of surgery and use of opioid analgesics (table 4). In both cases, the treatment groups were well matched for these factors (table 2). Of those patients who did not receive an opioid analgesic, 69.75% vomited, while only 40% of those who received an opioid analgesic vomited. There were no differences in patients' assessment of pain in the four groups. In general, no more than 15% of patients in each group experienced severe pain at any time.

The groups were comparable in time taken after operation to respond to verbal commands and time taken for return of bowel function. Similarly, there were no significant differences between the treatment groups in vital signs during the study or in haematological or biochemical variables. Nine patients had a two-fold elevation in hepatic enzymes after operation. Although this was of some clinical concern to the investigators, the incidence of increased concentrations of hepatic enzymes was well distributed among the four treatment groups. The most common adverse events were constipation,

Table 1 Patient characteristics (mean (range) or number (%))

	Placebo (n = 133)	Granisetron 0.1 mg (n = 132)	Granisetron 1.0 mg (n = 134)	Granisetron 3.0 mg (n = 128)
Males (n)	7	5	3	5
Females (n)	126	127	131	123
Premenopausal (%)	85 (67.5)	86 (67.7)	85 (64.9)	87 (70.7)
Luteal phase (%)	45 (52.9)	42 (48.8)	43 (50.6)	47 (54.0)
Age (yr)				
Mean (range)	48.5 (25–83)	46.8 (24–77)	48.0 (18–88)	46.1 (21–79)
Mean height (cm)	163.9	163.5	162.3	163.1
Mean weight (kg)	65.2	66.0	62.5	65.1

Table 2 Risk factors for postoperative nausea and vomiting (PONV) (number of patients (%))

Factor	Placebo (n = 133)	Granisetron 0.1 mg (n = 132)	Granisetron 1.0 mg (n = 134)	Granisetron 3.0 mg (n = 128)
Motion sickness	21 (15.8)	16 (12.1)	13 (9.7)	23 (18.0)
Previous history of PONV	43 (32.3)	35 (26.5)	23 (17.2)	39 (30.5)
Surgical procedure				
Gynaecological	117 (87.9)	117 (88.6)	119 (88.8)	119 (93.0)
Gastrointestinal	16 (12.0)	14 (10.6)	14 (10.4)	9 (7.0)
Not recorded	0 (0)	1 (0.8)	1 (0.8)	0 (0)
Opioid analgesics	114 (85.7)	112 (84.8)	109 (81.3)	105 (82.0)
Duration of anaesthesia (h)				
Median (range)	1.70 (0.41–6.66)	1.59 (0.53–4.90)	1.80 (0.40–5.50)	1.67 (0.45–4.56)
Time to recovery (h)				
Mean (range)	0.34 (0.00–3.41)	0.32 (0.05–2.75)	0.32 (0.00–2.75)	0.31 (0.01–2.16)

Table 3 Percentage of patients with no nausea, no vomiting or total control at 0–6 h and 0–24 h. ***$P < 0.001$ compared with placebo

	Placebo (n = 133)	Granisetron 0.1 mg (n = 132)	Granisetron 1.0 mg (n = 134)	Granisetron 3.0 mg (n = 128)
0–6 h				
No nausea	34.6	38.6	63.4***	57.0***
No vomiting	49.6	58.3	78.4***	76.6***
Total control	31.6	37.1	63.4***	54.7***
0–24 h				
No nausea	21.8	28.0	50.0***	42.2***
No vomiting	33.8	44.7	63.4***	61.7***
Total control	18.0	26.5	49.3***	42.2***

Table 4 Significance of treatment-by-factor interactions (*significant at the 10% level)

Factor	24-h response (P value)
Age	0.9429
Weight	0.6353
Surgical procedure	0.0638*
Previous history of PONV and/or motion sickness	0.2617
Pre- or post-menopausal	0.8426
Duration of anaesthesia	0.4712
Use of opioid analgesics	0.0773*
Use of anticholinergics	0.6265
Centre	0.9856

headache and abdominal pain, but there were no significant differences in their occurrence between the treatment groups.

Discussion

This double-blind study was designed to determine the efficacy of three different single doses of i.v. granisetron (0.1 mg, 1.0 mg, and 3.0 mg) compared with placebo in the prevention of PONV in patients undergoing open abdominal surgery or vaginal hysterectomy. Patients recruited into the study were a homogeneous group of mainly women undergoing gynaecological procedures, for whom PONV constitutes a well recognized problem [8–12]. The groups were well matched for known risk factors, such as sex, age, surgical and anaesthetic procedures, and the use of opioid analgesics. There was a slight imbalance between the groups with respect to history of PONV and motion sickness; this, however, did not affect the results of the study, as demonstrated by the treatment-by-factor analysis.

The results confirmed that PONV is common in these patients undergoing mainly gynaecological surgery, if no prophylactic antiemetic treatment is given, using a standard anaesthetic technique. Prophylactic administration of granisetron 1.0 mg or 3.0 mg resulted in a significant reduction in the numbers of patients who experienced postoperative vomiting during the periods 0–6 h and 0–24 h. The first episode of vomiting also occurred significantly later in the granisetron 1.0 mg and 3.0 mg groups than in the placebo group. Similar significant differences were seen in those patients who experienced no nausea or who achieved total control: doses of 1.0 mg and 3.0 mg were equally effective and both were significantly more effective than placebo. The granisetron 0.1 mg group was not significantly superior to placebo for any of the efficacy variables.

Use of rescue medication over the first 24-h period was less common in the granisetron 1.0 mg and 3.0 mg groups (24.6% and 22.7% of patients, respectively) than in the placebo group (39.8% of patients). Also, distribution of survival times to first use of rescue antiemetics differed significantly between the granisetron 1.0 mg and 3.0 mg groups and the placebo group, in favour of granisetron.

The majority of patients in each of the groups received opioid analgesics, but granisetron appeared to be effective whether or not opioids had been given. In either case, the response was most marked in the granisetron 1.0 mg group. The reduction by granisetron in the proportion of patients who vomited was less marked in patients who had received opioids because there was less likelihood of vomiting in these patients (as indicated by the placebo group) despite the known emetogenic potential of opioids. Evidence that effective pain relief can prevent nausea and vomiting may account for this finding [13].

An important side effect of currently used antiemetics (droperidol, metoclopramide and prochlorperazine) in the perioperative period is sedation, which has the potential for delaying recovery from anaesthesia. None of the three doses of granisetron used in this study caused any delay in recovery from anaesthesia. The study raised no concerns about the safety of granisetron. The safety profiles of the three doses of granisetron used in this study were similar to placebo in terms of adverse events and changes in vital signs, and haematological and biochemical variables. The side effects most commonly encountered were constipation and headache. Although both of these complaints are known to be associated with 5-HT_3 receptor antagonists [14], the incidence and severity of both events were similar to those in the placebo group.

These encouraging results are similar to those obtained with another 5-HT_3 receptor antagonist, ondansetron [7, 12, 15]. Moreover, direct comparison of granisetron and a classic antiemetic, the dopamine receptor antagonist, metoclopramide, has clearly demonstrated the superiority of granisetron [16]. Extrapyramidal effects may be a problem with dopamine antagonists and their absence with selective 5-HT_3 antagonists is a distinct advantage.

In conclusion, granisetron proved effective in the prevention of PONV. Our data do not suggest that increasing the dose from 1.0 mg to 3.0 mg confers any additional benefit; a dose–response plateau appeared to have been reached. We conclude, therefore, that 1.0 mg is the optimum dose. Further studies are required to compare the efficacy of granisetron with other commonly used antiemetics, and to define its role in patients undergoing different surgical procedures, particularly day surgery.

References

1. Blower PR. The role of specific 5-HT_3 receptor antagonism in the control of cytostatic drug-induced emesis. *European Journal of Cancer* 1990; **26** (Suppl. 1): S8–S11.
2. Newberry NR, Watkins CJ, Sprosen TS, Blackburn TP, Grahame-Smith DG, Leslie RA. BRL 46470 potently antagonizes neural responses activated by 5-HT_3 receptors. *Neuropharmacology* 1993; **32**: 729–735.
3. Elliott P, Seemungal BM, Wallis DI. Antagonism of the effects of 5-hydroxytryptamine on the rabbit isolated vagus nerve by BRL 43694 and metoclopramide. *Naunyn-Schmiedebergs Archives of Pharmacology* 1990; **341**: 503–509.
4. Marr HE, Davey PT, Bartlett AJ. Emerging differences between 5-HT_3 receptor antagonists. *Anti-Cancer Drugs* 1991; **2**: 513–518.
5. Cupissol DR, Serrou B, Caubel M. The efficacy of granisetron as a prophylactic anti-emetic and intervention agent in high dose cisplatin-induced emesis. *European Journal of Cancer* 1990; **26** (Suppl. 1): S23–S27.
6. Kovac A, McKenzie, R, O'Connor T, Duncalf D, Angel J, Gratz I, Fagraeus I, McLeskey C, Joslyn AF. Prophylactic intravenous ondansetron in female outpatients undergoing gynaecological surgery: a multicentre dose-comparison study. *European Journal of Anaesthesiology* 1992; **9** (Suppl. 6): 37–47.
7. Helmers JHJH. Oral ondansetron in the prevention of postoperative nausea and vomiting. *European Journal of Anaesthesiology* 1992; **9** (Suppl. 6): 49–54.
8. Lerman J. Surgical and patient factors involved in postoperative nausea and vomiting. *British Journal of Anaesthesia* 1992; **69** (Suppl. 1): 24S–32S.
9. Camu F, Lauwers MH, Verbessem D. Incidence and aetiology of postoperative nausea and vomiting. *European Journal of Anaesthesiology* 1992; **9** (Suppl. 6): 25–31.
10. Madej TH, Simpson KH. Comparison of the use of domperidone, droperidol and metoclopramide in the prevention of nausea and vomiting following major gynaecological surgery. *British Journal of Anaesthesia* 1986; **58**: 884–887.
11. Bodner M, White PF. Antiemetic efficacy of ondansetron after outpatient laparoscopy. *Anesthesia and Analgesia* 1991; 73: 250–254.
12. McKenzie R, Kovac A, O'Connor T, Duncalf D, Angel J, Gratz I, Tolpin E, McLeskey C, Joslyn A. Comparison of ondansetron versus placebo to prevent postoperative nausea and vomiting in women undergoing ambulatory gynecologic surgery. *Anesthesiology* 1993; **78**: 21–28.
13. Andersen R, Krohg K. Pain as a major cause of postoperative nausea. *Canadian Journal of Anaesthesia* 1976; **23**: 366–369.
14. Bunce KT, Tyers MB. The role of 5-HT in postoperative nausea and vomiting. *British Journal of Anaesthesia* 1992; **69**: (Suppl. 1): S60–S62.
15. Volpe N, Gesini A, Collini S, Sarli L, Grassano MT and the Investigators of the Italian Multicentre Ondansetron Study. Single dose ondansetron for prevention of postoperative nausea and vomiting. Results from the Italian Multicentre Ondansetron Study. *Drug Investigation* 1994; **8**: 67–72.
16. Fujii Y, Tanaka H, Toyooka H. Reduction of postoperative nausea and vomiting with granisetron. *Canadian Journal of Anaesthesia* 1994; **41**: 291–294.

British Journal of Anaesthesia 1996; **76**: 519–525

Rheological properties of commonly used plasma substitutes during preoperative normovolaemic acute haemodilution

G. FREYBURGER, M. DUBREUIL, M. R. BOISSEAU AND G. JANVIER

Summary

Preoperative normovolaemic acute haemodilution (PNAH) is used to reduce major blood loss during elective surgery. Considerable attention has been paid to colloid osmotic pressure, index of diffusibility and intravascular half-life of the currently available substitutes, but there is little information on their rheological properties from *in vivo* studies. Forty patients undergoing elective aortic reconstruction were given 4% human albumin (HA), 3.5% dextran 40 (Dxt 40), 6% dextran 60 (Dxt 60), 6% hydroxyethylstarch 200 (HES) or modified fluid gelatin (Gel) during PNAH to produce a packed cell volume (PCV) of approximately 30%. Mean volumes of more than 1000 ml were infused. Blood samples were obtained before infusion, immediately after, and 1.5 h after the end of haemodilution. The following variables were measured: PCV, plasma viscosity, whole blood viscosity at measured and corrected PCV (0.45), and erythrocyte aggregation. Haemodynamic and metabolic variables were determined at the same time. The five substitutes had very different effects on red blood cell aggregation and low shear rate viscosity at corrected PCV. Red blood cell aggregation was reduced in the presence of HA, Dxt 40, but was increased moderately to markedly in the presence of the other substitutes in the following order: HES < Dxt 60 < Gel. The influence of the rheological conditions on tissue oxygenation was assessed by measuring the concentration of lactic acid; this was unchanged after PNAH with HA or Dxt 40, but was increased in the presence of HES, Dxt 60 or Gel. (*Br. J. Anaesth.* 1996; **76**: 519–525)

Key words

Blood, haemodilution. Blood, substitutes. Blood, replacement. Surgery, vascular.

Preoperative normovolaemic acute haemodilution (PNAH) helps to reduce blood transfusion requirements in patients undergoing major surgery. PNAH reduces mean packed cell volume (PCV) leading to a decrease in blood viscosity. This in turn increases blood flow, assuming that the Hagen–Poiseuille equation is obeyed. The linear decrease in PCV results in an exponential improvement in the rheological properties of blood, particularly in the PCV range 30–46 %, with conservation of oxygen delivery from increased cardiac output despite the dilutional reduction in blood oxygen capacity [1]. As a result of dilution, blood lost during surgery contains plasma substitute, but fewer cells and plasma elements. The effective loss of blood constituents is thus considerably attenuated. Furthermore, autologous blood can be re-transfused after surgical bleeding has been controlled. In order to maintain normovolemia at reduced PCV, colloid diluents are required for intentional haemodilution.

PNAH has two main rationales: first, reduction in transfusion requirements (avoiding the risks of homologous transfusion) and second, improvement in circulatory state, particularly for patients at risk of ischaemia. Four main classes of colloid are used: (1) fractionated human albumin, (2) dextrans, (3) hydroxyethylstarch and (4) gelatins. Distribution, tissue storage, concentration half-life and effects on volume expansion and tissue oxygenation, and the relationship with haemostasis have been investigated for most of the current substitutes, but there is little information on their influence on blood rheology, a critical factor in microcirculatory perfusion. Blood rheology is influenced by quantitative factors, the concentration of red cells and proteins in plasma, but also by qualitative factors such as cell deformability and aggregation. Deformability has been found to be influenced little by pathological or pharmacological conditions.

In contrast, erythrocyte aggregation is commonly modified in certain conditions. It tends to occur at the very low shear rates encountered in the venous circulation, where most thrombi occur. In whole blood, red blood cell aggregation results from cross-linking of cells via interactions of their membranes with plasma fibrinogen, globulins and macromolecules. An energetic equilibrium is set up between the aggregation forces (adhesive properties of the macromolecules, where plasma substitutes operate) and repulsive forces (electrical charges on the red blood cell surface and shear stress). Erythrocyte aggregation is in fact a complex variable because of its relationship with blood flow. Thus any variable

---

GENEVIÈVE FREYBURGER, MD, (Département d'Anesthésie-Réanimation II and Laboratoire d'Hématologie); MARC DUBREUIL, MD, GÉRARD JANVIER*, MD (Département d'Anesthésie-Réanimation II); MICHEL R. BOISSEAU, MD (Laboratoire d'Hématologie); INSERM U8, Université de Bordeaux II, Pessac-Bordeaux, France. Accepted for publication: November 13, 1995.

*Address for correspondence: Département d'Anesthésie-Réanimation II, Hôpital Cardiologique, 33460 Pessac, France.

modifying red blood cell aggregation may influence tissue perfusion by slowing down circulation and reducing capillary flow.

In this study, we assessed, in patients undergoing elective surgery, the intrinsic rheological effects of different plasma substitutes, chosen from the four major families of plasma substitutes. PNAH is a good condition for the investigation of plasma substitutes *ex vivo*, in view of the standardized operative conditions, the large volumes of infusion required to attain the desired PCV and the requirement for optimal microcirculatory flow.

Patients and methods

After obtaining approval from the Institutional Human Investigation Committee and written informed consent, we studied 40 male patients undergoing elective aortic reconstruction (32 aortic aneurysms, eight arterial occlusions, mean age 62 (range 35–79) yr. Exclusion criteria were: unstable coronary disease, severe hypertension (i.e. treated with a combination of two different types of antihypertensive drugs), past history of cerebrovascular accident, chronic renal failure, haematological diseases, preoperative PCV $< 30\,\%$ and antiplatelet agents or antithrombotic treatment.

A standardized anaesthetic technique was used comprising propofol 2 mg kg^{-1}, fentanyl 5 μg kg^{-1} and atracurium 0.5 mg kg^{-1} at induction. After tracheal intubation, the lungs were ventilated (100–120 ml kg^{-1} min^{-1}) using a Siemens Servo 900B (Siemens Malmø, Sweden) with an FI_{O_2} of 0.5 (air/oxygen). Propofol 300–500 mg h^{-1}, fentanyl 0.25–0.5 mg h^{-1} and atracurium 0.2 mg kg^{-1} (when T4/T1 > 25 %) were used for maintenance of anaesthesia. Monitoring included ECG with ST segment analysis, Sp_{O_2}, capnography, pulmonary arterial catheter and radial artery cannula. Blood was obtained from a large venous catheter. PNAH was started 10 min after induction to produce a PVC of $\approx 30\,\%$, as calculated according to the rule of Manel and colleagues [2]. Volumes of blood withdrawn were replaced by equivalent volumes of substitutes and re-transfused at the end of surgery.

Fifty patients were allocated randomly to one of five groups. Incomplete medical records in 10 patients (three in each of the dextran and gelatin groups and one in the human albumin group) were discarded. Each group received a different plasma substitute: 4 % human albumin (HA) (Crts Bordeaux, France); 40000 molecular weight 3.5 % dextran (Plasmacair) (Dxt 40); 60000 molecular weight 6 % dextran (Hemodex) (Dxt 60); 6 % hydroxyethylstarch 200000 (Elohes) (HES) and modified 3 % gelatin (Plasmion) (Gel). The solvent for all solutions was normal saline. Patients given Dxt 40 and Dxt 60 received 20 ml of monovalent hapten dextran (average molecular weight = 1000 Da) (Promit), before infusion of the substitute. PCV was determined during haemodilution in the operating room by a micro-method (Autocrit II, Microspin Anaesthesia). Figure 1 shows the monitoring schedule for the haemodynamic measurements and blood sampling. Haemodynamic and lactic acid measurements were made before induction of anaesthesia and before PNAH (Ta), after induction of anaesthesia and before PNAH (Tb) and half-way through (Tc) and at the end of PNAH (Td). Measurements included: heart rate, mean arterial pressure, cardiac output, Sv_{O_2} and Sa_{O_2}. Blood samples for laboratory tests (anticoagulated with EDTA for the rheological tests) were obtained before PNAH (T0), at the end of PNAH, which lasted for approximately 30 min (T1), and 1.5 h after the end of PNAH (T2), as there appears to be some latency in haemostatic [3] or rheological [4, 5] effects.

Plasma and blood viscosity were measured at 37 °C in a Contraves LS 30 rotational viscometer. Whole blood viscosity was evaluated over a wide range of shear rates (seven shear rates) to cover all physiological conditions, but only "low" (1 s^{-1}) and "high" (128.5 s^{-1}) shear rates are shown in the results. The low shear rate is found in the venous circulation where aggregation mechanisms are predominant, and high shear rates are encountered in the arterial circulation where cell deformability is the predominant mechanism. Plasma, a Newtonian fluid, was examined at a single shear rate (128.5 s^{-1}). Because of the primary dependence of whole blood viscosity on PCV, viscosity was calculated at standardized PCV (0.45) according to the mathematical model described by Matrai, Whittington and Ernst [6] from the expression $\eta \times (\text{rel } 0.45) = (\eta \ (\text{rel PCV}))^{(0.45/\text{PCV})}$ where $\eta \times (\text{rel } 0.45)$ and η (rel PCV) are the viscosities of whole blood relative to plasma at standardized (0.45) and measured PCV, respectively. This model provides an estimate of the qualitative effects of the plasma substitutes independently of the quantitative effect of the decrease in cell concentration.

Erythrocyte aggregation at 37 °C was measured in a Sefam erythro-aggregometer (Vandoeuvre-les-Nancy, France) [7]. The main characteristics of the device and the significance and calculation of the variables studied have been described previously [8]. This apparatus measures the change in back-scattered light on abrupt cessation of suspensions of red blood cells (at different shear rates). The formation of red blood cell aggregates is indicated by a decrease in the optical signal. Several variables can be derived from the plot of light intensity as a function of time, and we determined: primary aggregation time (PAT), corresponding to the reverse of the slope of the curve between 0.5 and 2 s after cessation of maximum shear. This value decreases with increasing erythro-aggregation; partial disaggregation threshold (PDT) corresponds to dissociation of "*rouleaux*", and is calculated from the maximum intensity of back-scattered light as a function of shear rate. PDT increases as erythro-aggregation increases. The normal ranges for our laboratory have been established from samples taken from 20 normal volunteers (aged 20–60 yr); for PAT and PDT, they are 3 (0.5) s and 55 (10) s^{-1} respectively.

Erythrocyte deformability was studied using a Technicon helium–neon laser ektacytometer (Bayer-Technicon, Tarrytown, New York) combining a concentric viscometer and a light scattering device

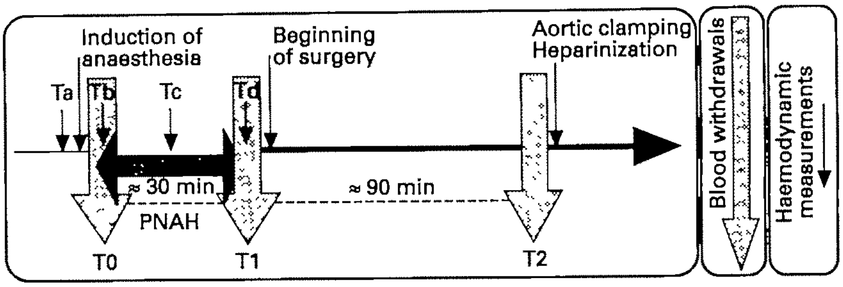


Figure 1 Monitoring schedule for haemodynamic measurements and blood sampling. Haemodynamic and lactic acid measurements were made before induction of anaesthesia and before PNAH (Ta), after induction of anaesthesia and before PNAH (Tb), and half-way through (Tc) and at the end of PNAH (Td). Blood samples were obtained before PNAH (T0), at the end of PNAH (T1) and 1.5 h after the end of PNAH (T2).

allowing calculation of an elongation index (EI) reflecting the deformation capacity of erythrocytes subjected to a well-defined shear force [9]. PCV was measured by microcentrifugation (Autocrit II).

Lactic acid was assessed by pyruvate peroxidation (normal range 0.6–2.2 mmol litre^{-1}). Plasma proteins have been shown to interfere with the haemorheological tests, and therefore total protein (Lowry method) and fibrinogen (Von Clauss method) were measured.

For each laboratory variable, two-way analysis of variance for repeated measures was carried out to assess the "group", "time" and "group × time" effects. The F ratios of the mean squares were calculated with respect to the residual mean of the square, and each ratio was tested against the critical F value (as a function of the different degrees of freedom), to measure the significance of each test. $P < 0.05$ was considered significant for ANOVA. Values at T1 and T2 were compared with those at T0 in each group of patients using Student's t test for paired samples. Unpaired Student's t test was also used to compare the different substitutes with albumin at each time of sampling.

Results

The mean volumes infused were highly comparable between the groups, despite the intra-group dispersion because of the large inter-individual differences in weight and size. Thus high mean volumes (> 1000 ml) were infused (table 1).

Table 2 shows the rheological variables at different times for the five groups. The results of ANOVA are summarized, indicating the influence of the time of withdrawal, or of the substitute, or both, on the different variables studied. For the whole patient series, time of blood withdrawal influenced most of the variables studied, with the exception of the variables unaffected by dilution, such as viscosity at corrected PCV and the erythrocyte deformability index. The major effect of haemodilution was seen as a decrease in PCV, which had decreased to 26–29 % by the end of the procedure (after careful application of Manel's rule). PCV remained close to this level for at least 90 min. ANOVA did not suggest any differences between the groups.

Plasma viscosity was reduced significantly in the presence of HA and increased significantly in the presence of Dxt 60. Thus ANOVA showed a significant "substitute" effect but no "time" effect resulting from the different effects of the various substitutes at T1 and T2 (hypoviscous (HA) or hyperviscous (Gel, HES, Dxt 60) compared with plasma viscosity). These alterations arise from the direct effect of the intrinsic viscosities of the substitutes on overall plasma viscosity. The measured viscosities of these substitutes are given in table 3.

The elongation index, which reflects erythrocyte deformability, was not influenced by haemodilution. The effects of the blood substitutes on whole blood viscosity were evaluated over the two phases illustrated in figure 2.

The primary effect of haemodilution was a decrease in PCV, leading to a reduction in whole blood viscosity. HA, Dxt 40 and HES produced the greatest reductions in whole blood viscosity (approximately 70 % of the initial value at low shear rate, and 30–40 % of the initial value at high shear rates), while Dxt 60 and Gel had smaller effects, despite the comparable decrease in PCV. This discrepancy was attributed to the differences in intrinsic viscosities of the substitutes. Comparison of whole blood visco-

Table 1 Patient characteristics and volumes of the five blood substitutes infused (mean (SD) [range]). No significant differences between groups

	HA	Dxt 40	Dxt 60	HES	Gel
n	9	7	7	10	7
Age (yr)	55 [35–68]	64 [44–79]	60.5 [48–75]	62 [36–75]	65 [50–78]
Weight (kg)	69 (9) [61–75]	71 (12) [60–92]	63 (20) [37–97]	68 (12) [50–90]	68 (8) [55–76]
Size (cm)	174 (8) [162–185]	169 (8) [160–180]	164 (8) [152–175]	170 (4) [160–175]	170 (3.5) [163–175]
Mean volume infused (ml)	1075 (199) [700–1200]	1193 (148) [1000–1400]	1171 (264) [750–1500]	1160 (273) [750–1800]	1150 (167) [800–1300]

Table 2 Rheological variables (mean (SD)). The roles of the factors "substitutes" and "time" on the different variables were assessed using two-way analysis of variance (+ = significant, − = not significant). The significance of the differences between values at T1 and T2 and those at T0 (Student's *t* test) were: $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$

	HA	Dxt 40	Dxt 60	HES	Gel	ANOVA	
						Time	Group
Packed cell volume (%)							
T0	38.8 (4.4)	37.1 (6.0)	38.9 (3.8)	39.4 (3.4)	39.1 (5.4)		
T1	29.3 (2.9)***	27.4 (5.4)***	26.1 (6.0)**	27.8 (4.4)***	28.8 (6.5)***	+	−
T2	28.5 (2.3)***	30.6 (3.6)**	24.7 (2.5)***	28.0 (3.6)***	28.8 (4.8)***		
Viscosity (mPa s^{-1})							
Plasma							
T0	1.45 (0.13)	1.41 (0.13)	1.47 (0.10)	1.38 (0.11)	1.47 (0.21)		
T1	1.31 (0.07)**	1.39 (0.08)	1.62 (0.16)*	1.44 (0.15)	1.47 (0.14)	−	+
T2	1.31 (0.12)*	1.40 (0.13)	1.60 (0.19)	1.41 (0.08)	1.50 (0.17)		
Whole blood velocity at 1 s^{-1}							
T0	15.98 (3.81)	13.77 (7.06)	15.58 (3.09)	14.70 (5.60)	14.98 (7.82)		
T1	4.32 (1.47)***	5.38 (3.03)*	10.48 (7.56)	5.74 (3.27)***	10.86 (4.67)	+	−
T2	4.58 (2.06)***	4.98 (2.43)*	7.82 (1.76)**	5.90 (3.35)***	8.73 (3.9)**		
Calculated at PCV 45%							
T0	23.80 (6.25)	18.52 (5.99)	20.74 (2.37)	20.71 (8.52)	19.47 (7.10)		
T1	8.01 (3.45)***	10.54 (4.75)**	27.95 (8.47)	12.49 (8.84)**	37.70 (27.3)*	−	+
T2	7.93 (5.78)***	10.42 (6.16)*	26.77 (9.94)	12.88 (7.76)*	21.70 (8.66)		
Whole blood velocity at 128.5 s^{-1}							
T0	4.42 (0.49)	4.08 (0.81)	4.15 (0.33)	4.33 (0.60)	4.65 (1.60)		
T1	3.20 (0.45)***	3.19 (0.53)**	3.65 (0.88)	3.25 (0.54)***	3.53 (0.59)*	+	−
T2	3.12 (0.31)***	3.49 (0.36)	3.32 (0.39)***	3.17 (0.37)***	3.39 (0.7)*		
Calculated at PCV 45%							
T0	5.31 (0.61)	5.05 (0.38)	4.90 (0.38)	5.17 (0.95)	5.38 (1.50)		
T1	5.11 (0.88)	5.38 (0.29)	6.34 (0.91)**	5.23 (0.82)	6.15 (2.14)	−	−
T2	5.16 (0.60)	5.38 (0.50)	6.02 (0.74)*	5.08 (0.44)	5.24 (1.00)		
Ektacytometry							
Elongation index							
T0	0.52 (0.03)	0.52 (0.04)	0.50 (0.03)	0.55 (0.04)	0.50 (0.10)		
T1	0.53 (0.02)	0.53 (0.04)	0.52 (0.04)	0.55 (0.05)	0.51 (0.11)	−	−
T2	0.53 (0.03)	0.53 (0.04)	0.53 (0.03)*	0.55 (0.05)	0.52 (0.08)*		
Erythroaggregation							
Primary aggregation time (s)							
T0	2.54 (0.49)	2.54 (0.34)	2.22 (0.63)	2.79 (1.35)	2.79 (1.21)		
T1	5.82 (12.99)**	6.73 (3.75)	3.25 (1.23)*	3.31 (1.25)	2.22 (0.79)	+	+
T2	6.17 (2.99)**	4.70 (1.50)*	2.90 (0.83)	3.47 (1.39)	1.92 (0.47)		
Partial dissociation threshold (s^{-1})							
T0	59.6 (15.6)	60.2 (12.9)	61.6 (15.6)	58 (18.1)	71.7 (31.7)		
T1	50.2 (11.9)*	59.1 (13.7)	92.9 (44.9)	81.6 (0.6)***	110.9 (31.1)**	+	+
T2	52.7 (19.0)**	54.9 (17.9)	112.5 (27.5)*	85 (0.5)***	130.3 (016.1)**		
Variables liable to interfere with rheological variables (g litre^{-1})							
Total protein							
T0	61.3 (5.6)	58.5 (5.8)	63.2 (1.9)	63.5 (9.4)	54.9 (14.4)		
T1	53.5 (1.7)**	50.7 (9.5)	48.6 (17.5)	47.6 (15.2)**	45.1 (10.3)*	+	−
T2	53.5 (0.6)*	51.0 (5.1)**	46.0 (17.9)	48.7 (11.5)**	44.7 (10.2)*		
Fibrinogen							
T0	3.6 (0.7)	3.1 (0.8)	4.2 (0.8)	2.8 (0.9)	3.4 (1.3)		
T1	2.6 (0.5)**	2.1 (0.7)**	2.5 (0.8)**	1.7 (0.6)***	2.4 (1.1)***	+	−
T2	2.6 (0.4)**	2.3 (0.6)**	2.2 (0.8)***	1.7 (0.5)***	2.3 (0.8)**		

Table 3 Intrinsic viscosity of the five substitutes

	HA	Dxt 40	Dxt 60	HES	Gel
Intrinsic viscosity (mPa s^{-1})	1	1.47	2.88	2.15	1.63

sities at corrected PCV, that is at constant PCV at the three times (T0, T1, T2), demonstrated more clearly the differences in intrinsic rheological effects of the different substitutes. The substitutes could be split into two main groups: HA, Dxt 40 and HES induced a dramatic reduction in corrected whole blood viscosity at low shear rates, whereas Dxt 60 and Gel markedly increased viscosity. At high shear rates there was no significant difference between the two groups of substitutes. Thus the major difference in the rheological effects of these substitutes was an effect on erythrocyte aggregation, a process occurring primarily at low shear viscosity.

Direct measurement of the characteristics of the erythrocyte aggregates (time to reform after dissociation and the force required to dissociate them) supported the viscosimetric findings. Two of the three substitutes from the first group (HA and Dxt 40), which reduced whole blood viscosity at corrected PCV, tended to increase the primary aggregation time and, to a lesser extent, reduce the forces required to dissociate the aggregates. In contrast, the second group of substitutes (Dxt 60 and Gel) induced hyperaggregation, reflected by the decrease in primary aggregation time for Gel and by

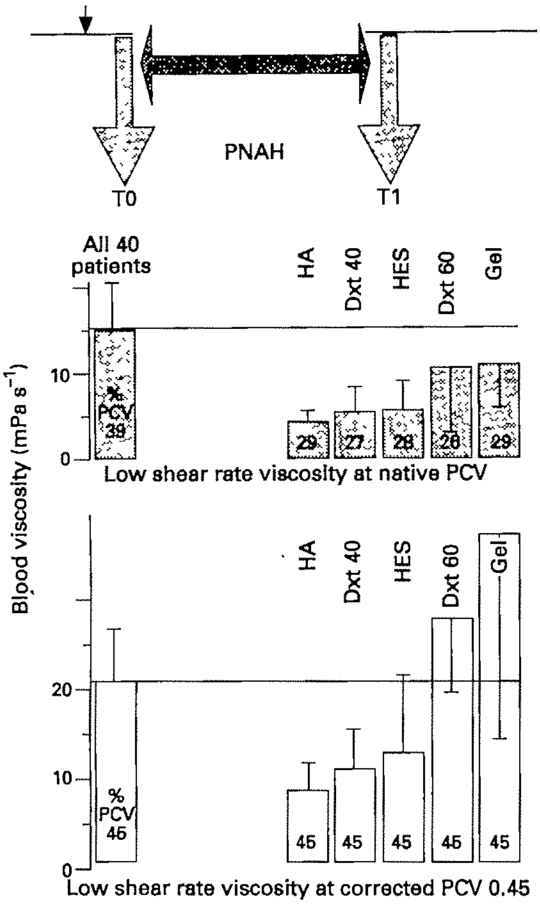


Figure 2 Modification of whole blood viscosity at low shear rate (1 s^{-1}) for native (top) and corrected (0.45 bottom) packed cell volume (PCV). Whole blood viscosity decreased as PCV decreased dramatically with haemodilution. The bottom histograms show the dramatic increase in whole blood viscosity at corrected PCV in the presence of Dxt 60 and Gel, demonstrating an intrinsic effect of these substitutes on red blood cell aggregation.

Table 5 Arterial lactic acid concentrations at T0 and T1 (mmol $litre^{-1}$) (mean (SD))

	HA	Dxt 40	Dxt 60	HES	Gel
T0	2.08 (0.59)	2.34 (0.61)	2.64 (0.69)	2.36 (0.49)	2.02 (0.44)
T1	2.13 (0.55)	2.39 (0.76)	2.86 (0.99)	3.00 (0.91)	3.24 (1.09)
P	ns	ns	ns	0.04	0.004

the increase in the partial dissociation threshold for both Dxt 60 and Gel. On the other hand, HES reduced whole blood viscosity (either at measured or corrected PCV), but tended to increase erythrocyte aggregation, as demonstrated by the significant increase in partial dissociation threshold observed. ANOVA showed the specific effect of the different substitutes on the variables involved in erythro-aggregation, namely low shear rate viscosity at corrected PCV, primary aggregation time and partial dissociation threshold.

Some variables that may interfere with the haemorheological test results were measured. Total protein and fibrinogen represent major determinants of plasma viscosity and erythrocyte aggregation, respectively. ANOVA showed a "time of withdrawal" effect but little difference between subgroups. The only difference was a smaller decrease in total protein content in the presence of albumin compared with the other substitutes.

The haemodynamic and metabolic data were analysed in the same way as the laboratory data. These variables obeyed their recognized time course during PNAH. ANOVA revealed few inter-group differences at either the first withdrawal (before anaesthesia and haemodilution) or on withdrawal at the end of haemodilution (T1) (table 4). There was a difference in heart rate between the groups at T1, because of the higher heart rate in the presence of Dxt 60 (compared with HA). Initial heart rate was also higher in this group before haemodilution (Ta), although the difference was not significant. Mean arterial pressure was lower after infusion of gelatin.

The influence of the different substitutes used during PNAH on tissue oxygenation was evaluated from the concentration of lactic acid, which reflects overall cellular oxygenation (table 5). Thus lactic

Table 4 Haemodynamic data (heart rate (HR), mean arterial pressure (MAP), pulmonary wedge pressure (PWP), cardiac index (CI) and oxygen consumption ($\dot{V}o_2$) (mean (SD)). One-way ANOVA was used at Ta (before anaesthesia to rule out predilution differences between groups) and at T1 (at the end of haemodilution to assess a substitute effect). $^*P < 0.05$

	HA	Dxt 40	Dxt 60	HES	Gel	ANOVA
HR (beat min^{-1})						
Ta	65.3 (4.9)	65.1 (9.4)	78 (13)	69.6 (9.5)	65.4 (6.2)	ns
T1	63.3 (5.3)	56.3 (7.9)	75 (9.2)	62.6 (9.7)	65.1 (16.5)	*
MAP (mm Hg)						
Ta	107.8 (10.4)	99.5 (17.6)	103.6 (11.2)	115.3 (12.8)	105.2 (7.5)	ns
T1	84.6 (14.4)	79.4 (16)	92.6 (24.4)	87 (7.5)	64.9 (6)	*
PWP (mm Hg)						
Ta	6.7 (4)	6.2 (3.2)	4 (3.5)	7.9 (3.5)	6 (5.6)	ns
T1	8.7 (4)	10 (3.6)	10 (7.5)	12 (2.1)	3.8 (5.5)	ns
CI (litre min^{-1} m^{-2})						
Ta	3.1 (0.6)	3 (1)	3 (0.7)	2.9 (0.6)	3 (0.5)	ns
T1	3 (0.4)	2.6 (0.9)	2.6 (0.5)	2.7 (0.4)	2.9 (0.7)	ns
$\dot{V}o_2$ (ml min^{-1} m^{-2})						
Ta	107 (15)	100.7 (18.9)	124.1 (50.6)	128.9 (23.2)	123.6 (7.9)	ns
T1	96.6 (26)	76.8 (43)	67.6 (47.7)	81.7 (10.8)	89 (31.2)	ns
Oxygen extraction (%)						
Ta	20.5 (4.4)	21 (4.9)	22.5 (5.9R)	25.1 (2.7)	24.8 (2.2)	ns
T1	25.2 (4.4)	23.6 (6.4)	20 (9.1)	25.8 (5.8)	26.5 (8.5)	ns

acid was increased significantly at the end of haemodilution by two (HES and Gel) of the three substitutes which had been shown to increase erythrocyte aggregation at T1. It was also increased by Dxt 60, although this was not statistically significant, mainly because of the higher initial values in this group of patients. Neither HA nor Dxt 40 had any effect on arterial lactic acid concentrations.

Discussion

We found that the salient effect of haemodilution was a significant improvement in whole blood rheology reflected by the immediate and sustained decrease in PCV and blood viscosity. The dramatic decrease in PCV was caused mainly by the high volumes infused (more than 1 litre). Albumin was chosen as a reference substitute as it is the closest substitute to plasma, with a homogeneous molecular weight. Because of the PCV value targeted (0.30), the need to maintain predilution blood volume to preserve an appropriate right heart filling pressure prevented us from using Ringer's solution as a control in view of the lack of volume-sustaining capacity of crystalloids.

The main finding was the markedly different effects of the different substitutes on whole blood viscosity as a result of their differing influences on red blood cell aggregation. Measured whole blood viscosity depends primarily on red cell concentration, which evaluated simply by measurement of PCV. Thus the effect of PCV needs to be taken into account in order to assess the other determinants of blood viscosity, such as red blood cell deformability and aggregation. We therefore calculated blood viscosity at a standardized PCV (0.45). Two (HA and Dxt 40) of the five substitutes were shown to improve the rheological properties, and two others (Dxt 60 and Gel) led to significant alterations. Similar results have been obtained by Audibert and colleagues [10] with HA, Dxt 40 and Gel. The low aggregating effect of Dxt 40 *in vitro* has been reported by Seike and Maeda Shiga [11]. On the other hand, Dxt 60 and Gel have also been shown to facilitate red blood cell aggregation *in vitro* by reducing the electrostatic repulsive forces after adsorption on the cell membranes [12, 13].

HES had a less consistent rheological effect with a decrease in low shear rate viscosity at corrected PCV and no change in aggregation time, in spite of increased cohesion of the aggregates (increased PDT). In ASA I patients, Dewachter and colleagues [5] reported no effect on blood viscosity at corrected PCV or on erythrocyte aggregation after infusion of HES 500 ml. Audibert and colleagues [10] observed results similar to ours on erythrocyte aggregation (also measured by the SEFAM instrument) after infusion of 1000 ml. The rheological response to HES may therefore depend on the amount infused. In a similar study in atherosclerotic patients, Ehrly Seebens and Saeger-Lorenz [14] demonstrated an increase in erythro-aggregation in the presence of 10% HES 200 500 ml (HES 50 g), although no comparable effect was observed in the presence of 6% HES 200 (HES 30 g). In our study, patients received a mean infusion volume of 1185 ml of 6% HES 200 (HES 71 g). An increase in red blood cell aggregation may thus occur above a critical concentration. Adding the same proportion of 6% HES 200 or of autologous plasma to a control blood (final PCV = 0.34) *in vitro*, there was a marked change in the aggregation variables in the presence of HES with a decrease in the primary aggregation time (1.87 s in the presence of HES *vs* 2.87 s in the presence of autologous plasma) and an increase in the partial dissociation threshold (97 s^{-1} *vs* 47.5 s^{-1}). As aggregation time was unchanged in our *ex vivo* study in spite of an increased dissociation threshold, there may be qualitative changes in the interactions between red blood cells and HES macromolecules transformed *in vivo* [15]. Goto and colleagues showed that in dogs, apart from an immediate and slight increase in the electrophoretic mobility of red cells indicating increased electronegativity, HES induced a delayed (after 12 h) reduction in electronegativity [16]. Gelatin has also been shown to interact specifically with plasma proteins such as fibronectin, and so may enhance the formation of bridges between red blood cells [17].

The rheological alterations and the influence of macromolecules on oxygen diffusion have an overall impact on tissue oxygenation, which should be reflected by the concentration of lactic acid. Changes caused by Dxt 60 were difficult to interpret because of the high initial concentrations of lactic acid in this group, but HES and Gel were found to induce a significant increase in lactic acid concentrations. This could be related to a reduction in oxygen flux to peripheral cells. HES, by increasing the forces required to dissociate the aggregates, might also reduce oxygen flux from red cells to tissues by impeding its diffusion [18]. On the other hand, Gel increased dramatically whole blood viscosity at corrected PCV, enhancing erythrocyte aggregation and capillary plugging. Vicaut and colleagues recently described a significant decrease in the density of perfused capillaries in the presence of hyper-erythro-aggregation *in vivo* [19].

Our data indicated that Dxt 40 and HA were the most efficient substitutes in respect of blood rheology and lactic acid concentrations. The concentrations of lactic acid, an indicator of cellular function, would be worth monitoring during PNAH. The rheological properties of a plasma substitute should be taken into consideration together with its volume expansive action. HES has questionable rheological qualities (partly because of its high substitution ratio) despite its well demonstrated and unchallenged expansive qualities. However, new hydroxyethylstarches with lower substitution ratios (0.4–0.5), equivalent concentration and low molecular weight will soon be available and these new products may demonstrate both acceptable rheological and wide-ranging qualities.

References

1. Messmer K, Kreimeier U, Intaglietta M. Present state of intentional haemodilution. *European Surgery Research* 1986; **18**: 254–263.
2. Manel J, Garric J, Lefevre JC, Laxenaire MC. Régle à calcul

du volume sanguin à prélever pour réaliser une hémodilution normovolémique intentionnelle. *Annales Françaises d'Anesthésie et de Réanimation* 1988; **7**: 427–432.

3. Bergqvist D. The influence of plasma volume expanders on initial haemostasis in the rabbit mesentery artery. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 607–609.
4. Jung F, Waldhausen P, Spitzer S, Mrowietz C, Hauser B, Wenzel E. Hämorheologische, mikro und makrozirulatorische effekte einer hypervolämischen hämodilutionmit mittelmolekularer hydroxyäthylstärke (Haes 200/0.62; 6%). *Infusiontherapie* 1988; **15**: 266–271.
5. Dewachter P, Laxenaire MC, Donner M, Kurtz M, Stolz JF. Effets rhéologiques in vivo des substituts plasmatiques. *Annales Françaises d'Anesthésie et de Réanimation* 1992; **11**: 516–525.
6. Matrai A, Whittington RB, Ernst E. A simple method of estimating whole blood viscosity at standardized hematocrit. *Clinical Hemorheology* 1987; **7**: 261–265.
7. Donner M, Siadat M, Stolz JF. Erythrocyte aggregation approach by light scattering determination. *Biorheology* 1988; **25**: 367–375.
8. Freyburger G, Janvier G, Dief S, Boisseau MR. Fibrinolytic and hemorheologic alterations during and after elective aortic graft surgery: Implications for postoperative management. *Anesthesia and Analgesia* 1993; **76**: 504–512.
9. Groner W, Mohandas N, Bessis M. New optical technique for measuring erythrocyte deformability with the ektacytometer. *Clinical Chemistry* 1980; **26**: 1435–1442.
10. Audibert G, Donner M, Lefèvre JC, Stolz JF, Laxenaire MC. Rheologic effects of plasma substitutes used for preoperative hemodilution. *Anesthesia and Analgesia* 1994; **78**: 740–745.
11. Seike M, Maeda Shiga T. Effect of plasma substitutes on the velocity of erythrocyte aggregation. *Japanese Journal of Transfusion Medicine* 1988; **34**: 420–431
12. Chien S, Jan KM. Red cell aggregation by macromolecules: role of surface adsorption and electrostatic repulsion. *Journal of Supramolecular Structure* 1973; **1**: 385–409.
13. Chien S, Simchon S, Abbott RE. Surface absorption of dextrans on human cell membrane. *Journal of Colloid Interface Science* 1977; **62**: 461–470.
14. Ehrly AM, Seebens H, Saeger-Lorenz K. Einflub einer 10%igen Hydroxyäthylstarkelösung (MG 20000/0,62) im vergleish mit einer 10%igen dextranlösung (MG 40000) auf die fliebeigenshaften des blutes und den gewebesauerstoffdruck von patienten mit claudicatio intermittens. *Infusiontherapie* 1988; **15**: 181–187.
15. Mischler JM. Synthetic plasma volume expanders—Their pharmacology, safety and clinical efficacy. *Clinics in Haematology* 1984; **13**: 75–92.
16. Goto Y, Sakakura S, Hatta M, Sugiura Y, Kato T. Haemorheological effects of colloidal plasma substitutes infusion. A comparative study. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 217–223.
17. Ballian G, Click E, Crouch E, Davidson J, Borstein P. Isolation of a collagen binding fragment from fibronectin and cold-insoluble globulin. *Journal of Biology and Chemistry* 1979; **254**: 1429–1433.
18. Morisaki H, Sibbald WJ. Issues in colloid and transfusion therapy of sepsis. In: Vincent JL, ed. *Year Book of Intensive Care and Emergency Medicine*. Berlin: Springer Verlag, 1993; 357–372.
19. Vicaut E, Hou H, Taccoen A, Decuypere L, Duveylleroy M. Red blood cell aggregation and microcirculation in the rat cremaster muscle. *International Journal of Microcirculation* 1994; **14**: 14–21.

British Journal of Anaesthesia 1996; **76**: 526–529

Rocuronium pretreatment reduces suxamethonium-induced myalgia: comparison with vecuronium

G. P. FINDLAY AND M. J. SPITTAL

Summary

We have studied, in 150 patients undergoing elective oral surgery, the effectiveness and sequelae of pretreatment with rocuronium for reducing myalgia after suxamethonium. Patients were allocated randomly to one of three groups: anaesthesia was induced with propofol and fentanyl, and group V received vecuronium 1 mg, group R rocuronium 6 mg and group P placebo pretreatment. Suxamethonium 1.5 mg kg^{-1} was given 60 s after the pretreatment agent. All patients received ketorolac 10 mg i.v. and morphine 10 mg i.m. for analgesia. The incidence of postoperative myalgia on day 1 after rocuronium (20%) was significantly less than after vecuronium (42%) ($P < 0.05$) or placebo (70%) ($P < 0.01$). By day 4 the incidence of myalgia was 28.6% in the rocuronium group, 46.3% in the vecuronium group and 95% in the placebo group. Intubating conditions were not affected adversely by any pretreatment regimen. (*Br. J. Anaesth.* 1996; **76**: 526–529)

Key words

Neuromuscular block, suxamethonium. Neuromuscular block, rocuronium. Neuromuscular block, vecuronium. Complications, myalgia.

Despite the recent introduction of short-acting, non-depolarizing neuromuscular blockers, suxamethonium, with its rapid onset of action, short duration of effect, complete and predictable paralysis, remains unsurpassed in providing ideal intubating conditions for tracheal intubation. However, since its introduction into clinical practice it has been recognized that myalgia occurs frequently in the postoperative period [1, 2]. Several strategies have been advocated to decrease the incidence of myalgia, one of the most successful being the administration of a small dose of non-depolarizing neuromuscular blocking drug before administration of suxamethonium [3, 4]. Various factors influence the efficacy of pretreatment, including the choice of non-depolarizing agent [5, 7], degree of prejunctional receptor block, interval between administration of pretreatment agent and suxamethonium, and speed of onset of the non-depolarizing drug. Rocuronium, which has a more rapid onset of action compared with established non-depolarizing agents [8], providing good intubating conditions within 60 s, has not yet been evaluated for the purpose of reducing suxamethonium-induced myalgia. As the optimum time interval for pretreatment with pre-existing drugs is approximately 3 min, this property of rocuronium may be relevant to its use in the prophylaxis of myalgia after suxamethonium.

The aim of this prospective, randomized, double-blind study was to assess the effect of rocuronium pretreatment on the frequency of suxamethonium-induced myalgia and to compare it with probably the most effective current pretreatment agent [4, 5, 7].

Patients and methods

After approval by the Hospital Ethics Committee and completion of written, informed consent, we studied 150 patients, aged 16–65 yr, ASA I or II. All patients were undergoing elective oral surgery under general anaesthesia necessitating tracheal intubation. We excluded patients who were assessed as possibly posing difficulty with tracheal intubation, using a combination of Mallampati's test and thyromental distance, and those considered unsuitable to receive the standard study anaesthetic technique.

All patients were premedicated with temazepam 0.3 mg kg^{-1}, to the nearest 10 mg, 1 h before operation. Anaesthesia was induced with fentanyl 1 μg kg^{-1} and a sleep dose of propofol. Patients then received vecuronium 1 mg (group V), rocuronium 6 mg (group R) or normal saline (group P), each made up to 2 ml. Fifty patients were allocated randomly to each pretreatment group and 60 s after pretreatment, patients received suxamethonium 1.5 mg kg^{-1}. Direct laryngoscopy was performed and the patient's trachea was intubated via the nasal route using an appropriately sized Magill tracheal tube, 60 s after suxamethonium. Anaesthesia was maintained with 1–2% isoflurane in oxygen-enriched air. Manual ventilation was adjusted to maintain normocapnia (Ohmeda 5200 carbon dioxide monitor) until commencement of spontaneous respiration. After induction of anaesthesia all patients received ketorolac 10 mg i.v. and morphine 10 mg i.m. for analgesia, and droperidol 500 μg i.v. as an antiemetic. The presence of fasciculations and their severity after suxamethonium were assessed on a four-point scale as: nil = no visible fasciculations,

---

G. P. FINDLAY*, MB, CHB, FRCA, M. J. SPITTAL†, MB, BS, FRCA, Department of Anaesthesia, Princess Alexandra's Hospital, Royal Air Force Wroughton, Swindon, Wiltshire SN4 0QJ. Accepted for publication: December 5, 1995.

Present addresses:

*Intensive Therapy Unit, University Hospital Wales, Heath Park, Cardiff CF4 4XW.

†Department of Anaesthesia, Princess Mary's Hospital, Royal Air Force Akrotiri, BFPO 57, Cyprus.

Table 1 Grading system for postoperative myalgia (after White [11])

Nil	No muscle pains or stiffness
Mild	Muscle pains or stiffness at one site but not causing disability or limiting activities
Moderate	Muscle pains or stiffness at more than one site but not causing disability or limiting activities
Severe	Muscle pains or stiffness at one or more sites and causing disability or limiting activities, e.g. difficulty getting out of bed or turning head

mild = very fine fingertip or facial muscle movements, moderate = minimal fasciculations on trunk and extremities, severe = vigorous fasciculations on trunk and extremities [9]. Overall intubating conditions were assessed as: excellent = intubation easy, no reaction from the patient, good = intubation resulting in slight coughing or bucking, poor = intubation possible, but resulting in more marked patient response [10]. The time taken to resumption of spontaneous respiration and duration of anaesthesia were noted.

Patients were visited on the first postoperative morning before discharge from hospital and interviewed by an investigator, blind to the pretreatment agent used, according to a structured questionnaire, as described by Erkola [5]. The presence and severity of myalgia were noted. Myalgia was graded on a four-point scale using the system described by White [11] (table 1). At the end of the interview, patients were given a second questionnaire, which was to be completed on day 4 after operation, and was designed to evaluate the incidence and severity of myalgia after discharge.

Patient characteristics and operative details were analysed using the independent samples *t* test. The incidence of myalgia and fasciculations was analysed using Fisher's exact test. Intubating conditions, severity of myalgia and severity of fasciculations were analysed initially using the Kruskal–Wallis test. If the Kruskal–Wallis test showed that significant differences existed between the groups then Dunn's multiple comparisons were performed to demonstrate which groups differed. $P < 0.05$ was considered significant.

Results

There were no significant differences in patient characteristics or operative details between the three groups (table 2).

Table 2 Patient data and operative details (mean (range or SD) or number). No significant differences (independent samples *t* test)

	Group V ($n = 50$)	Group R ($n = 50$)	Group P ($n = 50$)
Age (yr)	24.9 (17–46)	25.1 (19–40)	24.6 (17–48)
Weight (kg)	76.7 (11.6)	75.6 (12.2)	78.8 (13.5)
Sex (M:F)	39:11	38:12	40:10
Propofol induction dose (mg)	194 (26)	198 (28)	203 (30)
Duration of surgery (min)	26 (9)	28 (7)	25 (8)
Duration of apnoea (min)	7.1 (1.9)	7.1 (2.9)	7.3 (2.1)

Table 3 Incidence and severity of fasciculations. **$P < 0.01$ *vs* groups V and P (Fisher's exact test)

	Group V ($n = 50$)	Group R ($n = 50$)	Group P ($n = 50$)
None	8	46	0
Mild	11	4	10
Moderate	13	0	21
Severe	18	0	19
Total incidence (%)	84	8**	100

Table 4 Intubating conditions. No significant differences (Kruskal–Wallis test)

	Group V ($n = 50$)	Group R ($n = 50$)	Group P ($n = 50$)
Good	47	47	49
Adequate	2	3	1
Poor	1	0	0

The incidence of fasciculations in group R was significantly less than that in groups V and P ($P < 0.01$) (table 3). Analysis of the severity of fasciculations revealed highly significant differences (Kruskal–Wallis statistic $H = 81.91$, $P < 0.001$) between the three groups. This test was logically followed by Dunn's multiple comparisons which showed significant differences in the severity of fasciculations between groups V and R ($P < 0.01$) and between groups R and P ($P < 0.01$), but no significant difference between groups V and P.

There were no significant differences in intubating conditions between the three groups (table 4). Analysis of the incidence of myalgia on the first postoperative day (table 5) revealed significant differences between groups V and R ($P < 0.05$), groups V and P ($P < 0.01$) and groups R and P ($P < 0.0001$). There were highly significant differences in the severity of myalgia on the first postoperative day between the three groups (Kruskal–Wallis statistic $H = 18.11$, $P < 0.001$) and therefore Dunn's multiple comparisons were performed which showed that only the difference between groups R and P was statistically significant ($P < 0.01$).

There were no significant differences in the response rate to the questionnaire on day 4 after operation with 41, 42 and 40 patients from groups V, R and P, respectively, returning completed questionnaires. Analysis of the incidence of myalgia by day 4, using pooled information from questionnaires on days 1 and 4 (table 5), revealed significant differences between groups V and P ($P < 0.0001$) and groups R and P ($P < 0.0001$). The difference between groups V and R was not significant. The Kruskal–Wallis test indicated highly significant differences in the severity of myalgia by day 4 between the three groups (Kruskal–Wallis statistic $H = 25.8$, $P < 0.001$) and therefore Dunn's multiple comparisons were performed which revealed that only the differences between groups V and P ($P < 0.025$) and groups R and P ($P < 0.001$) were statistically significant.

Table 5 Incidence and severity of myalgia. $^{**}P < 0.01$, $^{***}P < 0.001$ *vs* group P; $^{\dagger}P < 0.05$ *vs* group V

	Day 1			Day 4		
	Group V ($n = 50$)	Group R ($n = 50$)	Group P ($n = 50$)	Group V ($n = 41$)	Group R ($n = 42$)	Group P ($n = 40$)
None	29	40	15	22	30	2
Mild	14	6	24	10	8	26
Moderate	6	3	7	5	3	9
Severe	1	1	4	4	1	3
Total incidence (%)	42**	20***†	70	46.3***	28.6***	95

Discussion

Suxamethonium is the best drug for rapidly providing ideal intubating conditions for short procedures. However, the usefulness of suxamethonium is limited by the frequent occurrence of postoperative myalgia. This is often listed as a minor side effect of the drug but it may be one of the most distressing consequences of minor surgery for the patient. The incidence of myalgia varies from 20% to 85% [12, 13]. This is undoubtedly a reflection of the many factors which influence the occurrence of pain.

Of the many regimens which have been proposed as a means of reducing the incidence of myalgia [9, 14–19], the most effective and widely used method is pretreatment with a small dose of non-depolarizing neuromuscular blocker [20]. A review of the literature revealed that vecuronium was probably the best agent in this respect [4, 5, 7] and for this reason we chose to compare rocuronium with vecuronium. Previous studies have used vecuronium 1 mg [7]. We therefore accepted that dose and, based on potency ratios, calculated a rocuronium dose of 6 mg. Administration of pretreatment agents both on a weight-related basis [21] and on a fixed-dose regimen [6, 7] has been recommended, but we chose a fixed-dose regimen for ease of routine administration.

One of the main concerns regarding pretreatment with non-depolarizing agents is that intubating conditions may be affected adversely. It is therefore recommended that a larger dose of suxamethonium be given to those who are pretreated [22]. In this study we used suxamethonium 1.5 mg kg^{-1} and found that pretreatment had no effect on intubating conditions. It has been suggested that increasing the dose of suxamethonium is not associated with accentuation of its adverse effects [23] but recent work has refuted this [24]. We therefore acknowledge that the use of such a dose of suxamethonium in the placebo group may be responsible for the high incidence of myalgia.

Rocuronium pretreatment is particularly effective in reducing fasciculations after suxamethonium. In 92% of patients, fasciculations were absent and in this respect rocuronium was superior to vecuronium ($P < 0.01$). However, as in many previous studies, we found no correlation between strength of fasciculations and myalgia.

There has been much discussion about the interval between administration of the pretreatment agent and suxamethonium. Intervals of 2, 3 and 4 min, or longer, have been recommended [11, 23, 25]. Obviously such lengthy intervals, required by slow onset drugs, are impractical on busy operating lists. Our hypothesis that rocuronium, because of its rapid onset of action, would be effective at reducing myalgia when only a short interval was allowed appears to have been substantiated.

Rocuronium pretreated decreased the incidence of myalgia to 20% on the first postoperative day and to 28.6% by day 4. Compared with vecuronium this was significant on day 1 but not by day 4 ($P < 0.05$, $P = 0.15$, respectively). This may be a reflection of the small sample size as a reduction in myalgia from 46.3% with vecuronium pretreatment to 28.6% with rocuronium pretreatment may be considered clinically significant. A larger sample size may clarify this issue.

Using reduced doses of suxamethonium alone can decrease the incidence of myalgia. Using suxamethonium 0.5 mg kg^{-1}, Stewart, Hopkins and Dean [24] reported that 41% of patients complained of myalgia while Nimmo and colleagues [26], using suxamethonium 0.25 mg kg^{-1}, reported an incidence of 20%. Intubating conditions in both studies were good. It may be seen that the use of rocuronium pretreatment and suxamethonium 0.25 mg kg^{-1} alone produce very similar incidences of myalgia while providing satisfactory intubating conditions. We plan a future prospective study to evaluate which strategy is superior. It is interesting to note that the study by Nimmo and colleagues [26] included a group in which no neuromuscular blocking drugs were used and who experienced an incidence of myalgia of 28%. It may be that, no matter which strategy is used to reduce suxamethonium myalgia, significant reductions below this value are unlikely. Against this background the results obtained in our rocuronium group appear to be excellent.

Acknowledgement

We thank Mr P. Strike, Principal Statistician, Institute of Pathology and Tropical Medicine, Royal Air Force Halton, for statistical advice.

References

1. Bourne JG, Collier HOJ, Somers GF. Succinylcholine (succinoylcholine); Muscle relaxant of short action. *Lancet* 1952; 1: 1225–1229.
2. Churchill-Davidson HC. Suxamethonium (succinylcholine) chloride and muscle pains. *British Medical Journal* 1954; 1: 74–75.

3. Sosis M, Broad T, Larijani GE, Marr AT. Comparison of atracurium and d-tubocurarine for prevention of succinylcholine myalgia. *Anesthesia and Analgesia* 1987; **66**: 657–659.
4. Manchikanti L, Grow JB, Colliver JA, Canella MG, Hadley CH. Atracurium pretreatment for succinylcholine-induced fasciculations and postoperative myalgias. *Anesthesia and Analgesia* 1985; **64**: 1010–1014.
5. Erkola O. Effects of precurarisation on suxamethonium-induced postoperative myalgia during the first trimester of pregnancy. *Acta Anaesthesiologica Scandinavica* 1990; **34**: 63–67.
6. Bennetts FE, Khalil KI. Reduction of post-suxamethonium pains by pretreatment with four non-depolarising agents. *British Journal of Anaesthesia* 1981; **53**: 531–536.
7. Ferres CJ, Mirakhur RK, Craig HJL, Browne ES, Clark RJS. Pretreatment with vecuronium as a prophylactic agent against post-suxamethonium muscle pain. *British Journal of Anaesthesia* 1983; **55**: 735–740.
8. Booij LHDL, Knape HTA. The neuromuscular blocking effect of ORG 9426. *Anaesthesia* 1991; **46**: 341–343.
9. Hatta V, Saxena A, Kaul HL. Phenytoin reduces suxamethonium-induced myalgia. *Anaesthesia* 1992; **47**: 664–667.
10. Lund I, Stovner J. Dose–response curves for tubocurarine, alcuronium and pancuronium. *Acta Anaesthesiologica Scandinavica* 1970; **37S**: 238–242.
11. White DC. Observations on the prevention of muscle pains after suxamethonium. *British Journal of Anaesthesia* 1962; **34**: 332–335.
12. Foster CA. Muscle pains that follow the administration of suxamethonium. *British Medical Journal* 1960; **2**: 24–25.
13. Hegarty P. Post operative muscle pains. *British Journal of Anaesthesia* 1956; **28**: 209–212.
14. McLoughlin C, Elliott P, McCarthy G, Mirakhur RK. Muscle pains and biochemical changes following suxamethonium administration after six pretreatment regimes. *Anaesthesia* 1992; **47**: 202–206.
15. Gupte SR, Savant NS. Post-suxamethonium pains and vitamin C. *Anaesthesia* 1971; **26**: 436–440.
16. Collier CB. Dantrolene and suxamethonium. *Anaesthesia* 1979; **34**: 152–158.
17. Verma RS, Chatterji S, Mathur N. Diazepam and succinylcholine induced muscle pains. *Anesthesia and Analgesia* 1978; **57**: 295–297.
18. Kahraman S, Ercan S, Aypar U, Erdem K. Effect of preoperative intramuscular administration of diclofenac on suxamethonium induced myalgia. *British Journal of Anaesthesia* 1993; **71**: 238–241.
19. Baraka A. Self taming of succinylcholine induced fasciculations. *Anesthesiology* 1977; **46**: 292–293.
20. Laurence AS. Myalgia and biochemical changes following intermittent suxamethonium administration. Effects of alcuronium, lignocaine, midazolam and suxamethonium pretreatment on serum myoglobin, creatinine kinase and myalgia. *Anaesthesia* 1987; **42**: 503–510.
21. Wig J, Bali IM. Relation of precurarisation to suxamethonium to provide ease of intubation and to prevent post-suxamethonium muscle pains. *Canadian Anaesthetists Society Journal* 1979; **26**: 94–98.
22. Cullen DJ. The effect of pretreatment with non-depolarising muscle relaxants on the neuromuscular blocking action of succinylcholine. *Anesthesiology* 1971; **35**: 572–578.
23. Stoelting RK, Peterson C. Adverse effects of increased succinylcholine dose following d-tubocurarine pretreatment. *Anesthesia and Analgesia* 1975; **54**: 282–288.
24. Stewart KG, Hopkins PM, Dean SG. Comparison of high and low doses of suxamethonium. *Anaesthesia* 1991; **46**: 833–836.
25. Brodsky JB, Brock-Utne JG, Samuels SI. Pancuronium pretreatment and post-succinylcholine myalgia. *Anesthesiology* 1979; **51**: 259–261.
26. Nimmo SM, McCann N, Broome IJ, Robb HM. Effectiveness and sequelae of very low-dose suxamethonium for nasal intubation. *British Journal of Anaesthesia* 1995; **74**: 31–34.

British Journal of Anaesthesia 1996; **76**: 530–535

Carbon dioxide output in laparoscopic cholecystectomy

T. KAZAMA, K. IKEDA, T. KATO AND M. KIKURA

Summary

In pneumoperitoneum, carbon dioxide eliminated in expired gas (carbon dioxide output) contains both metabolic and absorbed carbon dioxide from the peritoneal cavity. When elimination of carbon dioxide is much higher than carbon dioxide output, storage of tissue carbon dioxide and arterial carbon dioxide concentrations change. Finally, the rate of carbon dioxide eliminated in expired gas is not a match for the real rate of metabolic production and absorbed carbon dioxide from the peritoneal cavity. During and after insufflation of carbon dioxide, changes in carbon dioxide output were elucidated under constant arterial carbon dioxide pressure (Pa_{CO_2}), the same as the preinduction level. We studied patients undergoing elective laparoscopic cholecystectomy. Carbon dioxide output, oxygen uptake, respiratory exchange ratio (RER), expired minute ventilation ($\dot{V}E$), deadspace to tidal volume ratio ($VD/\dot{V}T$ ratio) and arterial to end-tidal carbon dioxide partial pressure difference ($Pa_{CO_2}-PE'_{CO_2}$) were determined before induction, and during anaesthesia, pneumoperitoneum and recovery. By controlling ventilatory frequency (*f*) every 1 min, Pa_{CO_2} was adjusted to concentrations before induction. Constant monitoring of end-tidal carbon dioxide partial pressure (PE'_{CO_2}) and intermittent measurement of ($Pa_{CO_2}-PE'_{CO_2}$) (15-min intervals) were conducted to predict Pa_{CO_2}). Carbon dioxide output and oxygen uptake decreased significantly from mean values of 83.5 (SEM 5.2), 101.6 (5.1) to 68.5 (4.2), 81.1 (4.6) ml min^{-1} m^{-2} (ATPS, $P <$ 0.05) with sevoflurane anaesthesia, and RER did not change. During carbon dioxide pneumoperitoneum (intra-abdominal pressure 8 mm Hg), carbon dioxide output increased by 49% (102.4 (5.0) ml min^{-1} m^{-2}) ($P < 0.05$) while oxygen uptake remained stable and RER increased from 0.84 (0.02) to 1.16 (0.03) ($P < 0.05$). It was necessary to increase $\dot{V}E$ during pneumoperitoneum by 1.54 times that during anaesthesia to maintain individual Pa_{CO_2} values constant. After removal of carbon dioxide from the abdominal cavity, the regression equation of excess carbon dioxide output/BSA best fitted a two-compartment model. The time constants of the rapid and slow compartments were 8.2 and 990 min, respectively. Excess carbon dioxide output/BSA was still 5.5 ml min^{-1} m^{-2}, 30 min after pneumoperitoneum. (*Br. J. Anaesth.* 1996; **76**: 530–535)

Key words

Surgery, laparoscopy. Anaesthetics, volatile, sevoflurane. Ventilation, carbon dioxide response. Ventilation, deadspace. Oxygen, uptake.

Laparoscopic gynaecological procedures involve a short duration of intraperitoneal carbon dioxide insufflation and are performed usually in young or otherwise healthy female patients. Changes in haemodynamic state and arterial blood-gas tensions with insufflation of carbon dioxide have been studied extensively and found to be relatively insignificant [1–6]. However, peritoneal insufflation for laparoscopic cholecystectomy may be longer than that for gynaecological procedures.

Insufflation of the abdominal cavity with carbon dioxide may be associated with pulmonary atelectasis, decreased functional residual capacity and high peak airway pressures. Absorption of carbon dioxide via the peritoneum causes hypercapnia but not impaired ventilation in healthy patients [7, 8]. Significant carbon dioxide retention has been demonstrated in patients with cardiopulmonary impairment during carbon dioxide pneumoperitoneum for extended procedures such as laparoscopic cholecystectomy [7, 9], with possibly consequent cardiac arrhythmias [10]. In pneumoperitoneum, carbon dioxide eliminated in expired gas (carbon dioxide output) contains both carbon dioxide of metabolic production and also absorbed carbon dioxide from the peritoneal cavity. Although there has long been interest in the rate of carbon dioxide output during long-lasting laparoscopic procedures, the reported data [5, 10–12] are not consistent, possibly because storage of carbon dioxide may be variable.

This study was conducted to assess excess carbon dioxide output evoked by pneumoperitoneum with stable carbon dioxide storage maintained by keeping arterial Pa_{CO_2} constant at preinduction levels and to investigate continued carbon dioxide load after pneumoperitoneum using a pharmacokinetic model.

Patients and methods

We studied 12 consenting, ASA I or II patients, undergoing elective laparoscopic cholecystectomy.

TOMIEI KAZAMA, MD, KAZUYUKI IKEDA, MD, TAKASUMI KATO, MD, MUTSUHITO KIKURA, MD, Department of Anaesthesiology and Intensive Care, Hamamatsu University School of Medicine, 3600 Handa-cho, Hamamatsu, Japan 431-31. Accepted for publication: October 27, 1995.

Correspondence to T.K.

Approval was obtained from the Human Studies Committee at Hamamatsu University Hospital. Patients were in good general health, with no signs or laboratory findings of renal, pulmonary or hormonal disease, or obesity (defined as a body mass index > 29). All patients fasted overnight and were premedicated with hydroxygine 50 mg and atropine 0.5 mg 1 h before induction of anaesthesia. An i.v. cannula was inserted during local anaesthesia. I.v. infusion of sodium lactate solution was started, and the rate of infusion was adjusted to 8–10 ml kg^{-1} h^{-1} during the study. Heart rate and ECG were monitored continuously. An arterial cannula was inserted into the radial or dorsalis pedis artery during local anaesthesia for arterial pressure monitoring. An arterial blood sample was obtained from the indwelling arterial cannula anaerobically and analysed immediately (ABL 300 blood-gas analyzer, Radiometer, Copenhagen, Denmark). Rectal temperature was displayed continuously on a temperature module (Hewlett-Packard) using a thermistor probe inserted 10 cm into the rectum. Body temperature was maintained at 36–37 °C by external heating. The temperature of the operating room was maintained at 24–26 °C.

The sampling cannula for measuring end-tidal anaesthetic gas, oxygen, nitrogen and carbon dioxide concentrations was inserted between a micro-pore filter (Gambro Enström AB, Sweden) and the tracheal tube. Mean inspired and expired gas samples were obtained from bypass mini-mixing chambers mounted in each inspiratory and expiratory limb of the breathing circuit. These chambers have been described previously [13]. Gas samples from each chamber, and sampling cannula for end-tidal gas measurement were introduced individually into a mass spectrometer (MGA 1100, Perkin Elmer) calibrated against certified gas mixtures. The concentrations of oxygen, nitrous oxide, sevoflurane and nitrogen were measured at 1-min intervals. Expired minute volume was measured with an electric Wright respirometer placed in the expiratory limb, and calibrated previously against a dry gas of known composition at physiological flow. The accuracy was the same as that of the Fleisch pneumotachograph (Gould). Expired minute volume normalized for body surface area (BSA) was expressed at BTPS, and carbon dioxide output and oxygen uptake were expressed at STPD. Inspired minute volume was calculated by an inert tracer gas dilution technique [14–17]. Nitrogen was used as the "inert" gas and was included in the inspired gas during anaesthesia [16]. Pulmonary gas exchange was computed as follows: $\dot{V}\text{CO}_2 = \dot{V}\text{E}(F\text{E}_{\text{CO}_2} - F\text{I}_{\text{CO}_2} \times F\text{E}_{\text{N}_2}/F\text{I}_{\text{N}_2})$; $\dot{V}\text{O}_2 = \dot{V}\text{E}(F\text{I}_{\text{O}_2} \times F\text{E}_{\text{N}_2}/F\text{I}_{\text{N}_2} - F\text{E}_{\text{O}_2})$; $\text{RER} = \dot{V}\text{CO}_2/\dot{V}\text{O}_2$; where $\dot{V}\text{CO}_2$ = carbon dioxide output, $\dot{V}\text{O}_2$ = oxygen uptake, $F\text{I}$ and $F\text{E}$ = fractional mean concentrations of mixed inspired and expired gas, respectively; $\dot{V}\text{E}$ = expired minute volume and RER = respiratory exchange ratio. $F\text{I}_{\text{CO}_2}$, sampled from the mixing chambers, was measured by mass spectrometer in order to exclude the effect of ageing on carbon dioxide absorber. The equations for calculation are valid even in the presence of anaesthetic gas [15, 18]. The ratio of deadspace to tidal volume ($V\text{D}/V\text{T}$) was calculated using Bohr's equation [19]; $V\text{D}/V\text{T} = (P\text{a}_{\text{CO}_2} - P\text{E}_{\text{CO}_2})/P\text{a}_{\text{CO}_2}$, where $P\text{E}_{\text{CO}_2}$ = carbon dioxide partial pressure of mixed expired gas.

Before induction of anaesthesia, all subjects were permitted to breathe room air through the anaesthesia mask for 20 min and mean expired and inspired concentrations of oxygen, carbon dioxide, nitrogen and expiratory minute volume were measured to obtain baseline carbon dioxide output and oxygen uptake. Anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v. and non-depolarizing neuromuscular blocker (vecuronium 0.1 mg kg^{-1}). Tracheal intubation was performed orally using a cuffed tracheal tube. Inspired concentrations of oxygen, nitrogen and nitrous oxide were adjusted to 30%, 20% and 50%, respectively, during anaesthesia. The inspired sevoflurane mixture was adjusted to give an end-tidal sevoflurane concentration of 1.37% (0.8 MAC). The fresh gas flow rate was 6–7 litre min^{-1}. The lungs of all patients were ventilated mechanically with the same ventilator equipped with an anaesthesia machine (Narcomed3, North American Drager, USA). Tidal volume was set at 10 ml kg^{-1}. Ventilatory frequency (f) was adjusted mainly each minute to maintain $P\text{a}_{\text{CO}_2}$ at preinduction levels with continuous monitoring of end-tidal carbon dioxide pressure ($P\text{E}'_{\text{CO}_2}$) and intermittent measurement of arterial to end-tidal carbon dioxide partial pressure difference ($P\text{a}_{\text{CO}_2} - P\text{E}'_{\text{CO}_2}$). Arterial blood samples were obtained every 15 min after stabilization of the ventilator settings and analysed for pH, $P\text{a}_{\text{CO}_2}$, $P\text{a}_{\text{O}_2}$ and base excess. Before skin incision, baseline carbon dioxide output and oxygen uptake were obtained after they reached steady state. Neuromuscular block was maintained with additional increments of vecuronium 0.025 mg kg^{-1} when the train-of four ratio exceeded 75%. Carbon dioxide was introduced into the peritoneal cavity by a carbon dioxide Pneu (Wisap, Germany) pressure limiting automatic insufflation apparatus and abdominal pressure was maintained at 8 mm Hg in all patients. After insufflation, multiple incremental changes in minute volume were made to maintain $P\text{a}_{\text{CO}_2}$ at preinduction levels. The table was tilted about 5° of the reverse. Trendelenburg position and then slightly to the left lateral position. Laparoscopic cholecystectomy was performed by a standard procedure. Intraperitoneal gas was evacuated after cholecystectomy and regression of carbon dioxide output in the post-insufflation state was measured 30 min under stable $P\text{E}'_{\text{CO}_2}$ every 1 min by manual control of ventilatory frequency. After carbon dioxide output returned to control level, neuromuscular block was antagonized with neostigmine 2.0–2.5 mg i.v. and atropine 1.0 mg i.v. The trachea was then extubated.

Anaesthesia was divided into five periods: (1) preinduction phase, (2) anaesthesia phase (control period of anaesthesia before skin incision), (3) pneumoperitoneum phase (during laparoscopy at intra-abdominal pressure of 8 mm Hg), (4) post-pneumoperitoneum phase (0–30 min after evacuation of carbon dioxide from the peritoneal cavity), and (5) recovery phase (40 min after extubation).

To fit the regression curve for carbon dioxide output during the post-pneumoperitoneum phase to multicompartment models, the least squares method was used and the number of compartments was determined by minimum AIC (an information criterion) based on the maximum likelihood estimation method [20].

Statistical analysis was carried out using analysis of variance (ANOVA), Fisher's test and Student's *t* test, where appropriate. $P < 0.05$ was considered statistically significant. All values are expressed as mean (SEM).

Results

We studied 12 premedicated patients, who were essentially normal in the pre-anaesthesia state (table 1). Steady states for $\dot{V}CO_2$/BSA and $\dot{V}O_2$/BSA were obtained during the following phases: preinduction, anaesthesia, pneumoperitoneum and recovery. Although it was difficult to maintain Pa_{CO_2} constant during the 10 min after tracheal intubation and the start of surgery, $P\text{E}'_{CO_2}$ concentrations were maintained at 5.0–5.4 kPa.

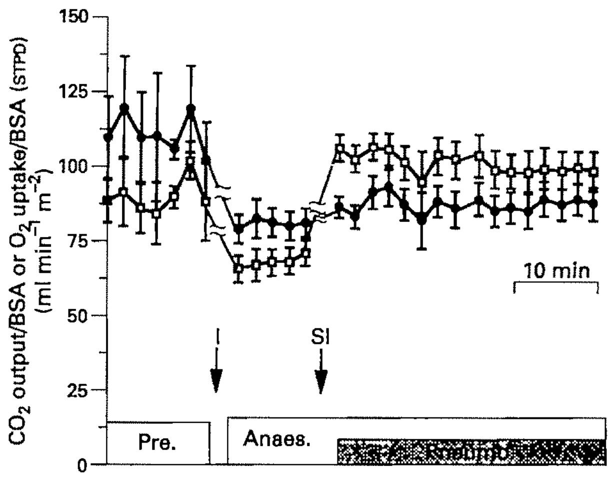


Figure 1 Changes in carbon dioxide output (□) and oxygen uptake (●) in the pre-induction (Pre.) anaesthesia (Anaes.) and pneumoperitoneum (Pneumo.) phases while maintaining $P\text{E}'_{CO_2}$ constant at the normal value for the preinduction phase (mean, SEM; $n = 12$). I = Intubation, SI = skin incision.

Compared with the preinduction phase, minute ventilation ($\dot{V}\text{E}$) decreased from 5.26 (0.33) to 3.33 (0.27) litre min^{-1} ($P < 0.05$) in the anaesthetic phase and increased to 5.14 (0.30) litre min^{-1} in the pneumoperitoneum phase ($P < 0.05$). Respiratory minute volume during pneumoperitoneum thus had to be made 1.54 times that in the anaesthesia phase to maintain Pa_{CO_2} constant (table 2). Carbon dioxide output and oxygen uptake decreased, respectively, from 83.5 (5.2), 101.6 (5.1) to 68.5 (4.2), 81.1 (4.6) ml min^{-1} m^{-2} (ATPS, $P < 0.05$) with sevoflurane anaesthesia and RER did not change. During pneumoperitoneum, carbon dioxide output increased 49 % (102.4 (5.0) ml min^{-1} min^{-2}, $P < 0.05$) while oxygen uptake remained stable and RER increased from 0.84 (0.02) to 1.16 (0.03) ($P < 0.05$, table 2, figs 1, 2). These variables returned to preinduction levels during recovery. Pa_{CO_2}, pH, base excess and Sa_{O_2} in the preinduction phase were normal (table 2) and were maintained throughout the experiment.

Table 1 Characteristics of patients, pneumoperitoneum (pneumo.) and anaesthesia (mean (SEM or range))

Age (yr)	Sex (M:F)	Weight (kg)	Height (cm)	Duration of anaesthesia (min)	Duration of pneumo. (min)	CO_2 volume for insufflation (litre)
52.5 (37–69)	5:7	57.1 (16.7)	154.1 (11.0)	196.2 (5.4)	89.3 (4.4)	77.2 (5.1)

Table 2 Metabolic and respiratory variables during the four phases of the procedures (mean (SEM)). $P\text{E}'_{CO_2}$ = end-tidal carbon dioxide pressure; $\dot{V}\text{E}$ = expired minute volume; $\dot{V}CO_2$/BSA = carbon dioxide output/body surface area; $\dot{V}O_2$/BSA = oxygen uptake/body surface area; RER = respiratory exchange ratio; $V\text{D}/V\text{T}$ = deadspace to tidal volume ratio; $(Pa_{CO_2} - P\text{E}'_{CO_2})$ = arterial to end-tidal carbon dioxide tension. * Significant difference from pre-induction, ** significant difference from anaesthesia

	Preinduction	Anaesthesia	Pneumo-peritoneum	Recovery (40 min after extubation)
$P\text{E}'_{CO_2}$ (kPa)	5.4 (0.11)	5.4 (0.12)	5.4 (0.06)	5.3 (0.13)
Sa_{O_2} (%)	98 (1.3)	99 (1.2)	99 (0.9)	98 (1.1)
Tidal volume (litre)	0.39 (0.033)	0.43 (0.028)	0.5 (0.033)	0.32 (0.031)
$\dot{V}\text{E}$(litre min^{-1})	5.26 (0.33)	3.33 (0.27)*	5.14 (0.3)**	5.6 (0.32)
$\dot{V}CO_2$/BSA (ml min^{-1} m^{-2})	83.5 (5.2)	68.5 (4.2)*	102.4 (5.04)**	86.5 (6.1)
$\dot{V}O_2$/BSA (ml min^{-1} m^{-2})	101.6 (5.0)	81.1 (4.6)*	88.8 (4.8)	103.6 (5.2)
RER	0.82 (0.013)	0.84 (0.015)	1.16 (0.025)**	0.83 (0.03)
End-tidal sevoflurane (%)	0	0.70 (0.09)*	1.69 (0.10)**	0.05 (0.01)
$V\text{D}/V\text{T}$	0.43 (0.017)	0.31 (0.02)*	0.32 (0.017)	0.42 (0.023)
$(Pa_{CO_2} - P\text{E}'_{CO_2})$ (kPa)	0.16 (0.11)	0.12 (0.09)	0.28 (0.16)	0.48 (0.29)***
pH	7.430 (0.005)	7.426 (0.009)	7.409 (0.009)	7.385 (0.014)
Pa_{O_2} (kPa)	11.7 (0.44)	18 (0.9)	19.8 (0.92)	10.8 (0.55)
Pa_{CO_2} (kPa)	5.6 (0.09)	5.5 (0.08)	5.6 (0.08)	5.7 (0.09)
Base excess	2.8 (0.5)	2.4 (0.5)	1.6 (0.9)	2.1 (1.0)

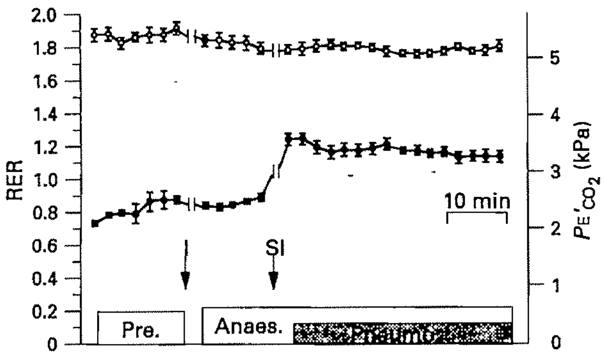


Figure 2 Changes in $P\text{E}'_{CO_2}$ (○) and respiratory exchange ratio (RER) (●) in the preinduction (Pre.), anaesthesia (Anaes.) and pneumoperitoneum (Pneumo.) phases (mean, SEM; $n = 12$). I = Intubation, SI = skin incision.

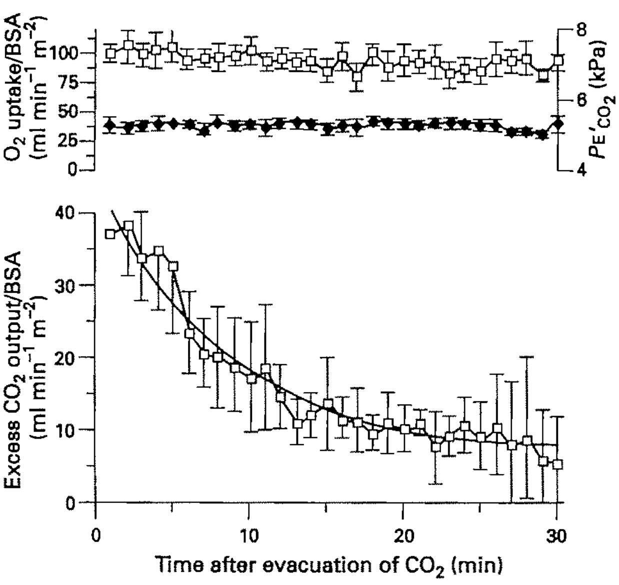


Figure 3 Changes in excess carbon dioxide output (□) after removal of carbon dioxide from the abdominal cavity. Oxygen uptake (□, top) and $P\text{E}'_{CO_2}$ (◆) were stable (mean, SEM; $n = 12$). ($Y = 39.4\,e^{-t/8.18} + 6.07e^{-t/990.13}$).

The results for haemodynamic state and temperature are summarized in table 3. After induction of anaesthesia there were decreases in heart rate, systolic arterial pressure, mean arterial pressure and diastolic arterial pressure. Significant increases in arterial pressure in the pneumoperitoneum phase were noted, but no cardiac arrhythmia was detected during induction, pneumoperitoneum or after pneumoperitoneum.

The regression equation for excess $\dot{V}CO_2$/BSA after removal of carbon dioxide from the abdominal cavity is shown in figure 3. $\dot{V}O_2$ and $P\text{E}'_{CO_2}$ were stable. A two-compartment model was judged to give the best fit by AIC. Excess carbon dioxide output pharmacokinetic variables and AIC values in each model are shown in table 4. Time constants of the first (rapid) and second (slow) compartments were 8.2 and 990 min, respectively. At the end of pneumoperitoneum, the rapid compartment was thought to be equilibrated, as $T_{\frac{1}{2}}$ was short (5.7 min) and carbon dioxide output was constant. The excess rate of carbon dioxide output/BSA was still 5.5 ml min^{-1} m^{-2}, 30 min after removal of carbon dioxide from the peritoneal cavity.

There was no clinical evidence of hypoxaemia, no change in standard bicarbonate before and after peritoneal insufflation, and no postoperative complications.

Discussion

During laparoscopy, the large volume of carbon dioxide for pneumoperitoneum is passively absorbed from the peritoneal cavity into the blood and most of it is removed from the circulation by hyperventilation. The respiratory effects of carbon dioxide absorbed from the peritoneal cavity into the blood have been studied previously [7, 21–27]. The quantity of carbon dioxide and bicarbonate ion in the body is large. When ventilation is not in accord with carbon dioxide output, hypercapnia continues. Sustained elevation in Pa_{CO_2}, typical of that associated with pneumoperitoneum, probably recruits whole-body storage depots, such as skeletal muscle and bone [28], in addition to intraperitoneal organs. Thus to study carbon dioxide output during laparoscopic cholecystectomy, the body storage of carbon dioxide must not be allowed to change. Although it is not certain that a constant Pa_{CO_2} necessarily implies constant storage, it is a reasonable assumption.

In the present study, $\dot{V}\text{E}$ was adjusted to maintain Pa_{CO_2} constant at the preinduction level with constant monitoring of $P\text{E}'_{CO_2}$ and intermittent measurement of (Pa_{CO_2}–$P\text{E}'_{CO_2}$). This method for estimating Pa_{CO_2} is invalid if the alveolar deadspace increases with ($Pa_{CO_2} - P\text{E}'_{CO_2}$), a situation that may occur during the period of carbon dioxide insufflation. Bramton

Table 3 Haemodynamic variables and temperatures during the four phases of the procedures (mean (SEM)). SAP = systolic arterial pressure; MAP = mean arterial pressure; DAP = diastolic arterial pressure; HR = heart rate. * Significant difference from preinduction; ** significant difference from anaesthesia

	Preinduction	Anaesthesia	Pneumo-peritoneum	Recovery (40 min after extubation)
SAP (mm Hg)	138.9 (4.0)	106.1 (1.7)*	130.9 (5.1)**	132.8 (3.7)**
MAP (mm Hg)	102 (3.7)	76.7 (1.4)*	101.9 (3.9)**	96.0 (3.5)**
DAP (mm Hg)	79.8 (3.5)	58.8 (1.3)*	73.9 (3.2)**	76.1 (3.2)**
HR(beat min^{-1})	75.5 (3.7)	67.6 (1.9)	76.0 (2.8)	70.1 (2.7)
Rectal temp.(°C)	36.48 (0.08)	36.49 (0.09)	36.46 (0.09)	36.45 (0.08)
Room temp.(°C)	26.2 (0.6)	25.9 (0.7)	25.5 (0.4)	25.4 (0.6)

Table 4 Excess carbon dioxide output pharmacokinetic variables and AIC values in each model. AIC = An information criterion [20]. $V1$, $V2$, $V3$ = volumes of each compartment, V^{ss} = total volume of distribution

	One-compartment model	Two-compartment model	Three-compartment model
A1	41.1	39.4	39
A2		6.1	1.8
A3			4.6
Time constant 1 (min)	13.2	8.2	8.2
Time constant 2 (min)		990	111
Time constant 3 (min)			1006
AIC	161.1	151.6	155.6
$V1$ (ml m^{-2})	543	323	320
$V2$ (ml m^{-2})		1849	1178
$V3$ (ml m^{-2})			1067
V^{ss} (ml m^{-2})	543	2172	2565

and Watson reported that monitoring of $P\text{E}'_{CO_2}$ during laparoscopy could be used to reflect Pa_{CO_2}, except at the start of pneumoperitoneum [29]. Fitzlerald and colleagues demonstrated that there were no changes in ($Pa_{CO_2} - P\text{E}'_{CO_2}$) during He pneumoperitoneum in mechanical ventilation [7]. In the present study, $V\text{D}/V\text{T}$ was almost constant except during preinduction when an anaesthesia mask was used for ventilation. Pa_{CO_2} during pneumoperitoneum was thought to be nearly constant, since $P\text{E}'_{CO_2}$ and $Pa_{CO_2} - P\text{E}'_{CO_2}$) were nearly constant (table 2, fig. 2).

During anaesthesia, the metabolic rate is reduced by about 15–30 % below that of the awake state [16, 30]. In this study, oxygen uptake and carbon dioxide output decreased 20.2 % and 18.0 % respectively. Thus RER remained constant, even during anaesthesia. Surgical stimulation may alter carbon dioxide output and oxygen uptake by increasing metabolic rate. End-tidal total MAC multiples of sevoflurane and nitrous oxide during pneumoperitoneum were maintained at 1.39, which was sufficient to prevent the effect of surgical stimulation on metabolism, as oxygen uptake did not change during surgery. The increased intra-abdominal pressure may have interfered with the elimination of carbon dioxide from abdominal organs and lower extremities by causing the veins to collapse. Carbon dioxide output and oxygen uptake increase after completion of pneumoperitoneum in this situation. However, an intra-abdominal pressure of 8 mm Hg, which was maintained automatically, did not hinder elimination of carbon dioxide, as oxygen uptake during and after pneumoperitoneum remained stable.

Marked increases in Pa_{CO_2} and excess carbon dioxide output, 66.9 mm Hg and 41 ml min^{-1}, respectively, 12 min after pneumoperitoneum were reported by Lewis and co-workers in young gynaecological patients anaesthetized with halothane during spontaneous ventilation [10]. Mullet and colleagues reported excess carbon dioxide output to be 32 ml min^{-1} with a 25 % increase in Pa_{CO_2} [12]. Wurst, Schulte-Steinbberg and Finsterer noted a 30–40 % increase in carbon dioxide output during pneumoperitoneum [11]. These values are less than the carbon dioxide output of 102.4 (5.0) ml min^{-1} m^{-2} and excess carbon dioxide output of 34.1 (3.9) ml min^{-1} m^{-2} (54.0 (4.6) ml min^{-1}) observed in the present study, possibly because of the following three factors: a decrease in tissue storage of carbon dioxide as a result of hyperventilation before insufflation of carbon dioxide, hypoventilation after insufflation and unstable conditions for measuring carbon dioxide output. Viale and colleagues demonstrated that the transient increase in RER at the start of anaesthesia was caused by increased carbon dioxide output during mechanical ventilation, as the standard controlled ventilation used (tidal volume = 10 ml kg^{-1}, ventilatory rate = 12 b.p.m.) may have caused alveolar hyperventilation. They found that 60 min was necessary to attain steady state after starting mechanical ventilation [15].

The regression equation for excess $V\text{CO}_2$/BSA showed the best fit with the two-compartment model (rapid and slow compartments) after removing carbon dioxide from the abdominal cavity. The half-times of the rapid and slow compartments were 5.7 and 686 min, respectively. A very small pressure difference causes carbon dioxide diffusion because carbon dioxide diffuses rapidly into the tissues. $P\text{CO}_2$ of arterial blood entering the tissues is 5.3 kPa; tissue capillary blood reaches almost complete equilibrium with interstitial $P\text{CO}_2$ when venous blood leaves the tissues [31]. The carbon dioxide insufflated to establish pneumoperitoneum diffuses into the abdominal organs and abdominal wall through the peritoneum, partly accumulates in tissue, and is then carried by the blood to the lungs. Therefore, the rapid compartment represents abdominal circulatory blood, liver, kidneys and other well-perfused tissues. The slow compartment represents tissues with low blood flow. Although the carbon dioxide load in the present study was clinically safe in patients without cardiac or pulmonary disease with controlled ventilation during and after pneumoperitoneum, excess $\dot{V}\text{CO}_2$/BSA was still 5.5 ml min^{-1} m^{-2}, 30 min after pneumoperitoneum. Therefore, patients receiving sedative drugs, patients with significant cardiac or pulmonary disease, or those with impaired ventilation in the pneumoperitoneum phase may be adversely affected by hypercapnia associated with carbon dioxide insufflation, even in the postoperative phase [9, 7].

Acknowledgements

We thank Koji Morita, PhD, and Yoshimitsu Sanjo, PhD for help and advice.

References

1. Kelman GR, Swapp GH, Smith I, Benzie RJ, Gordon NL. Cardiac output and arterial blood gas tension during laparoscopy. *British Journal of Anaesthesia* 1972; **44**: 1155–1162.
2. Smith I, Benzie RJ, Gordon NL, Kelman GR, Swapp GH. Cardiovascular effects of peritoneal insufflation of carbon dioxide for laparoscopy. *British Medical Journal* 1971; **3**: 410–411.
3. Motew M, Ivanovich AD, Bieniarz, Albrecht RF, Zabed B, Scommegna A. Cardiovascular effects and acid base and blood gas during laparoscopy. *American Journal of Obstetrics and Gynecology* 1973; **155**: 1002–1012.
4. Alexander GD, Brown EM. Physiologic alterations during pelvic laparoscopy. *American Journal of Obstetrics and Gynecology* 1969; **105**: 1078–1081.
5. Seed RF, Shakespeare TF, Muldoon MJ. Carbon dioxide homeostasis during anaesthesia for laparoscopy. *Anaesthesia* 1970; **25**: 223–231.
6. El-Minawi MF, Wahbi O, El-Bagouri IS, Sharawi M, El-Mallah SY. Physiologic changes during CO_2 and N_2O pneumoperitoneum in diagnostic laparoscopy. *Journal of Reproductive Medicine* 1981; **26**: 338–346.
7. Fitzgerald SD, Andrus CH, Baudendistel LJ, Dahms TE, Kaminski DL. Hypercarbia during carbon dioxide pneumoperitoneum. *American Journal of Surgery* 1992; **163**: 186–190.
8. Alexander GD, Noe FE, Brown EM. Anaesthesia for laparoscopy. *Anesthesia and Analgesia* 1969; **48**: 14–18.
9. Wittgen CM, Andrus CH, Fitzgerald SD, Baudendistel LJ, Dahms TE, Kaminski DL. Analysis of the hemodynamic and ventilatory effects of laparoscopic cholecystectomy. *Archives of Surgery* 1991; **126**: 997–1001.
10. Lewis DG, Ryder W, Burn N, Wheldon JT, Tacchi D. Laparoscopy—an investigation during spontaneous ventilation with halothane. *British Journal of Anaesthesia* 1972; **44**: 685–691.
11. Wurst H, Schulte-Steinbberg H, Finsterer U. Pulmonary elimination of carbon dioxide during laparoscopic cholecystectomy. *Anaesthesist* 1993; **42**: 427–434.
12. Mullet CE, Viale JP, Sagnard PE, Miellet CC, Ruynat LG, Counioux HC, Motin JP, Boulez JP, Dargent DM, Annat GJ. Pulmonary CO_2 elimination during surgical procedures using intra- or extraperitoneal CO_2 insufflation. *Anesthesia and Analgesia* 1993; **76**: 622–626.
13. Sanjo Y, Ikeda K. A small bypass mixing chamber for monitoring metabolic rate and anaesthetic uptake: The bymixer. *Journal of Clinical Monitoring* 1987; **3**: 235–243.
14. Aukburg SJ, Geer RT, Wollman H, Neufeld GR. Errors in measurement of oxygen uptake due to anesthetic gases. *Anesthesiology* 1985; **62**: 54–59.
15. Viale JP, Annat G, Bertrand B, Thouverez B, Hoen JP, Motin J. Continuous measurement of pulmonary gas exchange during general anaesthesia in man. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 691–697.
16. Brismar B, Hedenstierna G, Lundh R, Tokics L. Oxygen uptake, plasma catecholamines and cardiac output during neurolept–nitrous oxide and halothane anaesthesias. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 541–549.
17. Haneghan CPH, Gillbe CE, Branthwaite MA. Measurements of metabolic gas exchange during anaesthesia. *British Journal of Anaesthesia* 1981; **53**: 73–76.
18. Aukburg SJ, Geer RT, Wollman H, Neufeld GR. Errors in measurement of oxygen uptake due to anesthetic gases. *Anesthesiology* 1985; **62**: 54–59.
19. Nunn JF. Distribution of pulmonary ventilation and perfusion. In: *Applied Respiratory Physiology*, 3rd Edn. London: Butterworths, 1987; 141–183.
20. Akaike H. A new look at the statistical model identification. *IEEE Transactions on Automatic Control* 1974; **19**: 716–723.
21. Alexander GD, Noe FE, Brown EM. Anaesthesia for pelvic laparoscopy. *Anesthesia and Analgesia* 1969; **48**: 14–18.
22. Baratz RA, Karis JH. Blood gas studies during laparoscopy under general anesthesia. *Anesthesiology* 1969; **30**: 463–468.
23. Beremyi K, Fujita T, Siegler AM. Carbon dioxide laparoscopy: Anaesthetic management and determination of acid–base parameter. *Acta Anaesthesiologica Scandinavica* 1970; **14**: 77–80.
24. Desmond J, Gordon TA. Ventilation in patients anaesthetised for laparoscopy. *Canadian Anaesthetists Society Journal* 1970; **17**: 378–381.
25. Hodgson C, McClelland RMA, Newton JR. Some effects of the peritoneal insufflation of carbon dioxide at laparoscopy. *Anaesthesia* 1970; **25**: 382–387.
26. Lenz RJ, Thomas TA, Wilkins DG. Cardiovascular changes during laparoscopy. *Anaesthesia* 1972; **31**: 4–9.
27. Magno R, Medegard A, Bengtsson R, Transtad SE. Acid–base balance during laparoscopy. The effects of intraperitoneal insufflation of carbon dioxide and nitrous oxide on acid–base balance during controlled ventilation. *Acta Obstetrica Gynecologica Scandinavica* 1979; **58**: 81–85.
28. Nunn JF. Carbon dioxide. In: *Applied Respiratory Physiology*, 3rd Edn. London: Butterworths, 1987; 207–234.
29. Brampton WJ, Watson RJ. Arterial to end-tidal carbon dioxide tension difference during laparoscopy. Magnitude and effect of anaesthetic technique. *Anaesthesia* 1990; **45**: 210–214.
30. Nunn JF. Respiratory aspects of anaesthesia. In: *Applied Respiratory Physiology*, 3rd Edn. London: Butterworths, 1987; 350–378.
31. Guyton AC. Transport of oxygen and carbon dioxide in blood and body fluids. In: Guyton AC, ed. *Textbook of Medical Physiology*, 7th Edn. Philadelphia: Saunders, 1986; 493–503.

British Journal of Anaesthesia 1996; **76**: 536–543

LABORATORY INVESTIGATIONS

Effect of propofol and thiopentone on free radical mediated oxidative stress of the erythrocyte†

P. G. MURPHY, M. J. DAVIES, M. O. COLUMB AND N. STRATFORD

Summary

Propofol has free radical scavenging properties similar to those of recognized phenol-based antioxidants. We have examined these properties in an *in vitro* model of radical-induced cellular injury, comparing its activity with that of thiopentone (which has also been shown to have radical scavenging activity). Haemolysis of human erythrocytes was induced using the azo compound 2,2′-azo-bis(2-amidinopropane) dihydrochloride (ABAP). This was achieved by incubating a 10% suspension of erythrocytes with ABAP 100 mmol litre^{-1} at 37 °C. For propofol, at concentrations of 12.5, 25 and 50 μmol litre^{-1}, the times to achieve 50% haemolysis were mean 126 (SEM 7) min (95% confidence interval 108–144 min), 150 (8) (129–170) min and 182 (12) (160–180) min, respectively (Intralipid control 107 (7) (90–125) min, ANOVA $P < 0.0001$). For thiopentone, at concentrations of 62.5, 125 and 250 μmol litre^{-1}, the values were 117 (2) (112–121) min, 126 (3) (119–133) min and 138 (2) (132–144) min, respectively (saline control 109 (2) (104–113) min, ANOVA $P < 0.0001$). Spectroscopic analysis in the visible and ultraviolet spectra demonstrated a steady increase in the proportion of methaemoglobin during haemolysis, with the highest concentrations in the propofol-containing flasks. The formation of methaemoglobin was preceded by the generation of ferrylhaemoglobin (a Fe^{4+} haemoglobin species). Further experiments examining oxidation of purified methaemoglobin to ferrylhaemoglobin by hydrogen peroxide suggested that propofol, but not Intralipid or thiopentone, reduced ferrylhaemoglobin back to the met- state, and thereby explained the higher concentrations of methaemoglobin in the propofol-containing erythrocyte suspensions. We conclude that propofol is a more potent free radical scavenger in this model of oxidant stress than thiopentone, and that reduction of high oxidation states of haemoglobin may contribute to such activity. (*Br. J. Anaesth.* 1996; **76**: 536–543)

Key words

Anaesthetics i.v., propofol. Anaesthetics i.v., thiopentone. Blood, haemoglobin. Blood, erythrocytes. Blood, haemolysis.

Membrane peroxidation is regarded as a major mechanism whereby free radicals damage biological tissue [1]. Radical-mediated peroxidation of erythrocyte membranes leads to haemolysis and can be induced by a variety of reactive oxygen species, such as hydrogen peroxide [2] superoxide anion [3] and peroxyl radicals derived from the thermal decomposition of water-soluble and lipid-soluble azo compounds [4, 5]. The latter compounds provide an easily reproducible and reliable model of radical-induced haemolysis [4] and have demonstrated the importance of the endogenous lipid-soluble free radical scavenger α-tocopherol (vitamin E) in protecting the erythrocyte membrane against such injury [6]. The intracellular contents of the erythrocyte may also be susceptible to oxidant stress. For example, the haem-based iron of ferrous haemoglobin (Hb-Fe^{2+}) undergoes electron transfer reactions to form higher oxidation states such as met- (Hb-Fe^{3+}) and ferryl- (Hb-Fe^{4+}) haemoglobin species:

$$\text{Hb-Fe}^{2+} \leftrightarrow \text{Hb-Fe}^{3+} + e^- \leftrightarrow \text{Hb-Fe}^{4+} + e^- \quad (1)$$

The formation of higher oxidation states of haemoglobin has been described when erythrocytes are exposed to superoxide anion [3] and hydrogen peroxide [3, 7], although not when haemolysis is initiated by azo compounds [6].

The anaesthetic agent 2,6-diisopropylphenol is a potent antioxidant, chemically similar to α-tocopherol [8–10], and as such is a potent inhibitor of lipid peroxidation [8, 9]. In the *in vitro* experiments reported here, we have examined the effect of the clinical formulation of 2,6-diisopropylphenol, that is propofol, on peroxidation of erythrocytes induced by the water-soluble azo compound 2,2′-azo-bis(2-amidinopropane) dihydrochloride (ABAP). This has been evaluated in terms of haemolysis (as a measure of membrane integrity) and the haemoglobin redox state (as a measure of intracellular oxidant stress). The latter experiments showed that considerable quantities of met- and ferrylhaemoglobin are formed during ABAP-induced haemolysis, and that propofol significantly interferes with such redox reactions. In

---

P. G. MURPHY, FRCA, M. O. COLUMB, FRCA, Department of Anaesthesia, General Infirmary at Leeds, Great George Street, Leeds LS1 3EX. M. J. DAVIES, DPHIL, Department of Chemistry, University of York, Heslington, York, YO1 5DD. N. STRATFORD, FRCA, University Department of Anaesthesia, Southmead Hospital, Bristol. Accepted for publication: November 29, 1995.

†Presented in part at the Anaesthetic Research Society, Leeds Meeting (*British Journal of Anaesthesia* 1995; **75**: 229–230P) and at the Intensive Care Society.

Correspondence to P.G.M.

order to characterize this hitherto unreported property, we have examined the effect of propofol on the oxidation of purified methaemoglobin by hydrogen peroxide. As thiopentone has also been shown to have antioxidant properties (inhibiting lipid peroxidation *in vitro* [11]), we have also examined the relative activity of these two anaesthetic agents in this model of oxidant-induced cell injury.

Materials and methods

HAEMOLYSIS EXPERIMENTS

Preparation of RBC suspensions

Heparinized blood obtained on the day of experiment from six healthy, non-smoking volunteers was used for these studies (age range 25–35 yr, four males). After separation from plasma and buffy coat by centrifugation for 5 min at 4000 rpm, erythrocytes were washed three times with sterile NaCl 0.15 mmol litre^{-1}. During the last wash the cells were centrifuged for exactly 10 min at 4000 rpm to ensure a constant packed cell volume. The cells were then resuspended in four volumes of phosphate-buffered saline (PBS, NaCl 125 mmol litre^{-1}, Na_2HPO_4 10 mmol litre^{-1}, pH 7.4) to prepare a stock 20% RBC suspension.

Induction of free radical-mediated haemolysis

Free radical-mediated haemolysis of the RBC suspensions was initiated with ABAP (Polysciences). ABAP (R–N=N–R) is a water-soluble azo compound which although stable at 4 °C decomposes at 37 °C to produce organic radicals (R·, reaction 2) at a steady rate:

$$R\text{–}N\text{=}N\text{–}R \rightarrow 2R\cdot + N_2 \qquad (2)$$

These radicals react with molecular oxygen to produce organic peroxyl radicals ($RO_2\cdot$; reaction 3)

$$R\cdot + O_2 \rightarrow RO_2\cdot \qquad (3)$$

which initiate peroxidative damage to membrane proteins and lipids, and thereby induce haemolysis. For example, organic peroxyl radicals react with unsaturated lipid (LH) to produce lipid radicals (L·) and organic hydroperoxides (ROOH):

$$RO_2\cdot + LH \rightarrow ROOH + L\cdot \qquad (4)$$

In our experiments haemolysis was induced by mixing equal volumes of ABAP (200 mmol litre^{-1} dissolved in PBS) and 20% RBC suspensions to produce 10% RBC suspensions in ABAP 100 mmol litre^{-1}. The suspensions were incubated at 37 °C under aerobic conditions and agitated gently throughout. Aliquots were obtained every 30 min for measurement of percentage haemolysis and spectroscopic analysis.

Measurement of haemolysis

The extent of haemolysis in the RBC suspensions was measured spectrophotometrically, by comparing the extracellular haemoglobin content of the aliquots with that of a fully haemolysed reference sample. Thus, 200 µl of RBC suspension was added to 3.8 ml of PBS and centrifuged for 4 min at 4000 rpm. The supernatant was added to an equal volume of Drabkin's reagent (stock solution, potassium ferricyanide 1.21 mmol litre^{-1}, potassium cyanide 1.54 mmol litre^{-1}, potassium dihydrogen phosphate 2.06 mmol litre^{-1}) in order to convert the various species of haemoglobin present to cyanmethaemoglobin, its most stable form. The absorption of this solution was measured at 540 nm. The fully haemolysed reference was prepared in the same way, except that the 200-µl aliquot was added to distilled water rather than PBS. Percentage haemolysis was measured according to the equation

$$\%\ \text{haemolysis} = A/B \times 100$$

where A = absorbance of the sample aliquot and B = absorbance of the fully haemolysed reference. A line plot of percentage haemolysis *vs* time was constructed, from which was estimated the time taken to achieve 50% haemolysis (H_{50}, min).

Experimental design

The effect of propofol (Diprivan, Zeneca) was examined at 2, 6-diisopropylphenol concentrations of 12.5, 25 and 50 µmol litre^{-1}. The Intralipid content of the 12.5- and 25-µmol litre^{-1} flasks was adjusted to equal that of the 50-µmol litre^{-1} flask, as was that of the Intralipid control flask. The effect of thiopentone was examined at 62.5, 125 and 250 µmol litre^{-1}, with the equivalent control containing PBS. In both cases, the agents were added to the 200-mmol litre^{-1} stock solution of ABAP immediately before mixing with the 20% RBC suspension. In order to exclude spontaneous haemolysis during the incubation period, a second (blank) control consisted of a 10% RBC suspension with propofol or thiopentone but without ABAP.

Spectroscopic analysis of RBC suspensions

Different haemoglobin species have different absorption spectra and can therefore be distinguished spectroscopically. We investigated qualitatively and quantitatively the changes in the proportions of various haemoglobin species present during haemolysis. Qualitative assessments were made from absorption scans, measured using a Pye Unicam SP8-500 scanning spectrophotometer (range 500–700 nm, scan speed 2 nm s^{-1}). The proportions of the various haemoglobin species present in the reaction mixtures were made by measuring the absorbance of the suspensions at set wavelengths (560, 577 and 630 nm), correcting for background absorbance measured at 700 nm, and applying the following equations:

$$[\text{oxy-Hb}] = 0.068425A_{577} - 0.001442A_{560} - 0.082173A_{630}$$

$$[\text{met-Hb}] = 0.041828A_{577} - 0.079247A_{560} + 0.318075A_{630}$$

$$[\text{ferryl-Hb}] = 0.095969A_{560} - 0.054490A_{577} - 0.046882A_{630}$$

where A = measured absorbance at each wavelength. These equations are similar to those described elsewhere for analysis of myoglobin [12] and were derived by solving the simultaneous equations for the measured absorbance at the given wavelengths set up using the following millimolar extinction coefficients for haemoglobin [13]: oxyhaemoglobin λ_{560} 8.6, λ_{577} 15.0, λ_{630} 0.17; methaemoglobin, λ_{560} 4.30, λ_{577} 4.45, λ_{630} 3.63; ferrylhaemoglobin, λ_{560} 14.1, λ_{577} 3.9, λ_{630} 3.0.

In further spectroscopic studies, we examined if this model of erythrocyte oxidative injury involved generation of transient intermediate ferrylhaemoglobin species such as $Fe^{4+} = O\text{-protein}\cdot$ and $Fe^{4+} = O$, which are known to be generated during oxidation of methaemoglobin by peroxides. These unstable and reactive species are difficult to detect in cellular systems, particularly in low concentrations. The latter can be "trapped" by Na_2S, which reacts with ferrylhaem species to form stable oxysulpho compounds which absorb strongly at 620 nm [14]. Thus, in these experiments, ABAP-induced haemolysis was carried out in the presence of Na_2S 8 mmol litre^{-1}. The presence of oxysulphohaemoglobin was identified by spectral scanning and quantified by measuring the change in absorption at 620 nm.

HAEMOGLOBIN OXIDATION EXPERIMENTS

Spectroscopic analysis of the red cell suspensions showed that ABAP-induced haemolysis was associated with generation of both met- and ferrylhaemoglobin. Furthermore, there was consistently more methaemoglobin in the flasks containing propofol than those containing Intralipid, saline or thiopentone. In order to test the hypothesis that this latter observation was a result of the reduction of ferrylhaemoglobin (formed during ABAP-induced oxidative stress of the erythrocyte) back to methaemoglobin, we examined the effect of propofol on the peroxidation of methaemoglobin by hydrogen peroxide (H_2O_2).

Human haemoglobin (Sigma), which we found to be more than 80 % methaemoglobin, was prepared as a 23-µmol litre^{-1} solution in PBS. Precipitates were removed by centrifugation and the pH adjusted to 7.4 with NaOH. It was then oxidized with an excess of H_2O_2 (H_2O_2:haem of 20:1), to which was then added either propofol 12.5 or 50 µmol litre^{-1}, Intralipid, saline or thiopentone. All reactions were carried out at room temperature. Using the equations described above, the proportions of oxy-, met- and ferrylhaemoglobin were measured before and after the addition of H_2O_2 and at 10-min intervals for 30 min after the subsequent addition of propofol, thiopentone, Intralipid or saline.

STATISTICAL ANALYSIS

Values are expressed as mean (SEM) and 95 % confidence intervals. The effects of propofol and thiopentone on the rates of haemolysis, as expressed by H_{50} values, were analysed using analysis of variance (ANOVA), using Bartlett's test to determine homogeneity of variances of the groups [15]. Differences between individual groups were compared using a two-tailed unpaired t test, to which a Bonferroni correction was applied, and quantified by confidence interval analysis. The relationship between drug concentration and H_{50} values was explored further by applying a post-test for linear trend to the rank-ordered ANOVA tables [16]. This latter test describes the relationship of the measured variable (in this instance H_{50}) to column number in the ANOVA table, and thereby allows the underlying relationship between concentration of drug and H_{50} to be investigated. The effect of propofol on H_2O_2-induced peroxidation of methaemoglobin was analysed using ANOVA and Bonferroni corrected t tests.

Results

HAEMOLYSIS EXPERIMENTS

The effects of propofol and thiopentone on ABAP-induced haemolysis are shown in figure 1 and table 1. Propofol delayed ABAP-induced haemolysis in a concentration-dependent manner, and while at the concentrations examined here complete haemolysis was eventually achieved, higher concentrations of propofol also suppressed the maximum degree of haemolysis observed (data not shown). Although thiopentone also delayed the onset of haemolysis, comparison of H_{50} values showed that its effect was less than that of propofol (table 1).

Spectroscopic analysis of the red cell suspensions

Spectral scanning of the reaction mixtures suggested a steady shift from oxy- to methaemoglobin during ABAP-induced haemolysis (fig. 2). A feature of this analysis was consistently greater absorption at 630 nm in the propofol-containing flask compared with that containing Intralipid. Quantitative spectroscopic analysis confirmed these findings (fig. 3). Thus there were significantly higher concentrations of methaemoglobin in the propofol flasks in comparison with the Intralipid-containing control. As

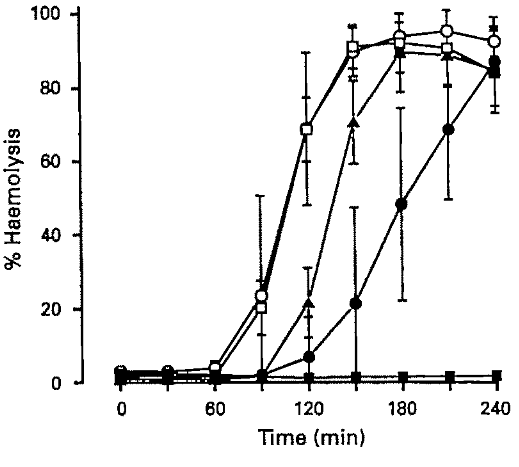


Figure 1 Effect of propofol 50 µmol litre^{-1} (●), Intralipid (□) and thiopentone 250 µmol litre^{-1} (▲) on ABAP-induced haemolysis (mean, 95 % confidence intervals, $n = 6$ in each case). ■ = Non-haemolysing control (erythrocyte suspension in PBS, no ABAP), ○ = haemolysing control.

Table 1 Effect of propofol and thiopentone on free radical-induced haemolysis. The rate of haemolysis is expressed as the time taken to achieve 50 % haemolysis (H_{50} (min), mean (SEM) (95 % confidence interval)). *ANOVA: $P < 0.0001$ (Bartlett's test for homogeneity of variances, $P = 0.57$). *t* test: Propofol 25 μmol litre^{-1} *vs* Intralipid, $P < 0.05$; propofol 50 μmol litre^{-1} *vs* Intralipid, $P < 0.001$; propofol 12.5 *vs* 50 μmol litre^{-1}, $P < 0.01$. Test for linear trend: $r^2 = 0.6634$, $P < 0.0001$. †ANOVA: $P < 0.0001$ (Bartlett's test for homogeneity of variances, $P = 0.73$). *t* test: Thiopentone 125 and 250 μmol litre^{-1} *vs* saline, $P < 0.001$; thiopentone 62.5 *vs* 125 μmol litre^{-1}, $P < 0.05$; thiopentone 62.5 *vs* 250 μmol litre^{-1}, $P < 0.001$; thiopentone 125 *vs* 250 μmol litre^{-1}, $P < 0.01$. Test for linear trend: $r^2 = 0.81$, $P < 0.0001$

	Intralipid	12.5 μmol litre^{-1}	25 μmol litre^{-1}	50 μmol litre^{-1}
Propofol*	107 (7) (90–125)	126 (7) (108–144)	150 (8) (129–170)	182 (12) (160–180)
	Saline	62.5 μmol litre^{-1}	125 μmol litre^{-1}	250 μmol litre^{-1}
Thiopentone†	109 (2) (104–113)	117 (2) (112–121)	126 (3) (119–133)	138 (2) (132–144)

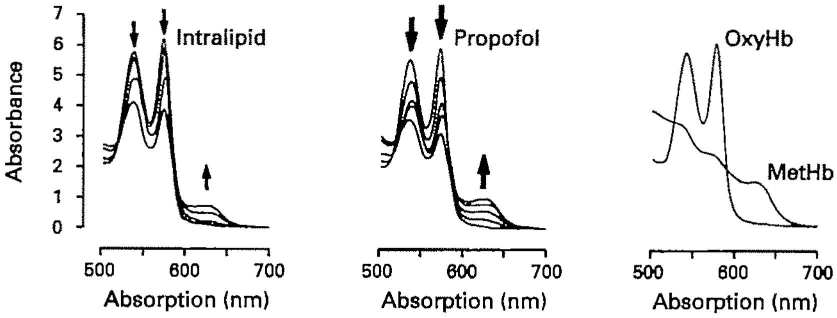


Figure 2 Sequential spectral absorption scans (absorption expressed in arbitrary units) of red cell suspensions containing Intralipid or propofol 50 μmol litre^{-1} during ABAP-induced haemolysis. Scans were performed every 60 min for 240 min and overlaid for ease of analysis. For comparison, the scans of pure oxy- (OxyHb) and methaemoglobin (MetHb) are shown. The direction of the changes in the sequential spectra are shown by the arrows. At time 0 both flasks contained predominantly oxyhaemoglobin. In the Intralipid flask there was little change before 180 min when the increase in absorption at 630 nm and the corresponding reduction in absorption at 540 and 577 nm suggest the formation of methaemoglobin. In comparison with Intralipid, the presence of propofol appeared to accelerate this transition from oxy- to methaemoglobin, with absorption at 630 nm being higher at any given time.

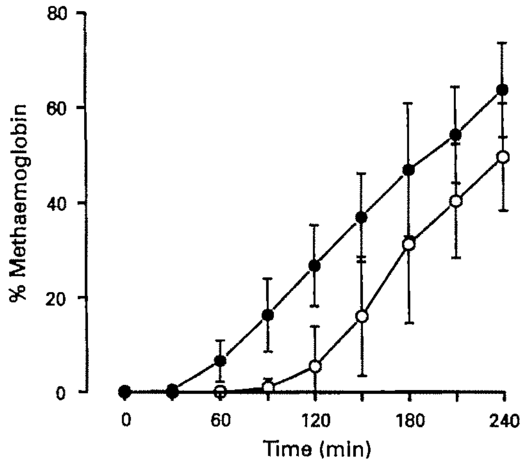


Figure 3 Effect of propofol 50 μmol litre^{-1} (●) and Intralipid (○) on the level of methaemoglobin measured by quantitative spectroscopic analysis during ABAP-induced haemolysis (expressed as percentage of total haem; mean, 95 % confidence intervals, $n = 6$). The effects of propofol 12.5 and 25 μmol litre^{-1} were intermediate between those of propofol 50 μmol litre^{-1} and Intralipid and were omitted for the sake of clarity. There was no difference between Intralipid and saline (the latter data were also omitted).

there was no difference between the concentrations of methaemoglobin in the Intralipid and saline flasks, this appeared to be an effect of propofol rather than Intralipid. Comparison of haemolysis and methaemoglobin data showed that while in the Intralipid-containing flasks methaemoglobin appeared only *after* cell lysis had started, in the propofol-containing flasks the appearance of methaemoglobin *preceded* haemolysis (fig. 4). In contrast with propofol, thiopentone had little effect of the concentrations of methaemoglobin (data not shown).

While confirming that oxidation of oxyhaemoglobin to the met- state had taken place, this quantitative analysis also suggested that in the early stages of haemolysis, 5–10 % of the total haemoglobin content was ferrylhaemoglobin (fig. 5). Furthermore, the proportion of this Fe^{4+} species was consistently lower in the presence of propofol in comparison with Intralipid. As relatively low concentrations of ferrylhaemoglobin were detected, it was felt important to obtain independent evidence for its generation during ABAP-induced haemolysis, using the sulphide-trapping method. Absorption at 620 nm (indicative of the reaction product of ferryl-

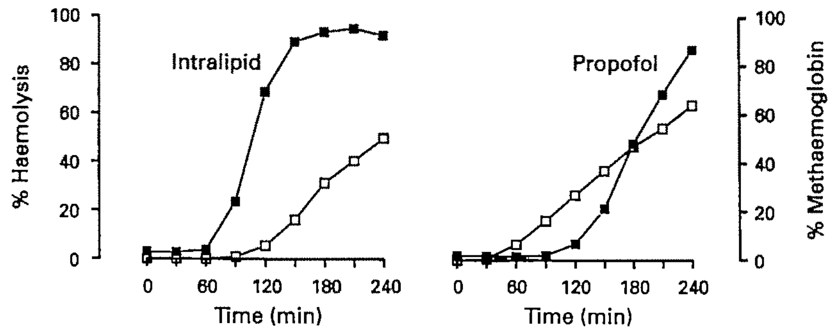


Figure 4 Effect of propofol 50 µmol litre^{-1} and Intralipid on the relationship between haemolysis (■) and increase in methaemoglobin (□) (mean, $n = 6$). In the Intralipid-containing flasks, haemolysis preceded significant methaemoglobin formation. In contrast, the presence of propofol, while delaying haemolysis, promoted the formation of methaemoglobin.

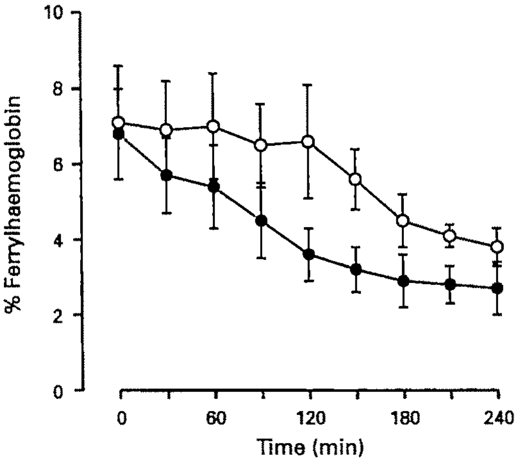


Figure 5 Changes in ferrylhaemoglobin concentrations during ABAP-induced haemolysis (expressed as percentage total haem; mean, 95% confidence intervals, $n = 6$ in each case). The concentrations of ferrylhaemoglobin in flasks containing propofol 50 µmol litre^{-1} (●) and an equivalent quantity of Intralipid (○) are shown. There was no difference in the concentrations of ferrylhaemoglobin between Intralipid- and saline-containing flasks, and the effect of intermediate concentrations of propofol (12.5 and 25 µmol litre^{-1}) was between the effects of propofol 50 µmol litre^{-1} and Intralipid (data not shown for the sake of clarity).

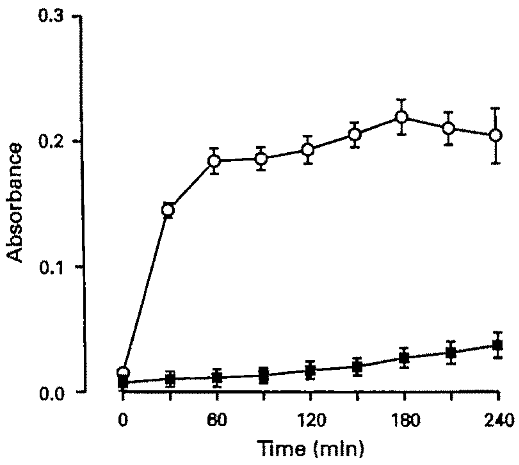


Figure 6 Absorption at 620 nm during ABAP-induced haemolysis in the presence of Na_2S 8 mmol litre^{-1} (mean, 95% confidence intervals) ○ = Saline, ■ = non-haemolysing control ($n = 6$).

haemoglobin and sulphide) increased rapidly in the red cell suspensions to which ABAP had been added, but only very slowly in the blank controls (fig. 6). Thus the formation of ferrylhaemoglobin during the early stages of the process was confirmed.

HAEMOGLOBIN OXIDATION EXPERIMENTS

The results of these experiments are shown in table 2. Oxidation of methaemoglobin with a 20-fold excess of H_2O_2 generated significant quantities of ferrylhaemoglobin, with a corresponding reduction in the proportion of methaemoglobin. Serial spectroscopic analysis over the subsequent 30 min demonstrated a gradual reduction in the concentration of the ferryl species accompanied by a corresponding increase in methaemoglobin concentrations. This transition was accelerated by propofol, but not by saline, Intralipid or thiopentone.

Discussion

Several workers have used models of oxidant-mediated haemolysis to investigate the susceptibility of intact cell membranes to oxidant stress and the efficacy of potential antioxidants, although the relationship between this and antioxidant activity in other tissues has not been well defined. Stocks and Dormandy, while commenting on the poor reproducibility of the assay, have shown that H_2O_2-induced haemolysis is inhibited by butylated hydroxyanisole and α-tocopherol [2], both established antioxidants. Haemolysis induced by azo compounds is much more predictable [4–6]. Using this model, Miki and co-workers have demonstrated in rats that dietary-induced deficiency of α-tocopherol enhances susceptibility to haemolysis induced by the water-soluble azo compound ABAP [6] and that antioxidants such as uric acid, ascorbic acid, cysteine, glutathione and water-soluble analogues of vitamin E confer protection *in vitro* [4]. The biochemical mechanisms underlying ABAP-induced lysis of erythrocytes are not defined, although recent studies suggest that radical-mediated injury to membrane lipids is not an important process in this model, and that damage to non-lipid membrane elements such as ion transport proteins is more likely to be responsible [17].

Table 2 Methaemoglobin oxidation experiments. Concentrations of met- and ferrylhaemoglobin (Hb) (expressed as percentage of total haem, mean (SEM) before and after oxidation of methaemoglobin with H_2O_2, and then 0, 10, 20 and 30 min after the subsequent addition of saline, Intralipid, thiopentone 250 μmol litre^{-1} or propofol 50 μmol litre^{-1}. Concentrations were analysed at each stage by one-way analysis of variance (ANOVA), and groups were compared with the propofol group using a *t* test to which a Bonferroni correction was applied ($*P < 0.05$, $**P < 0.01$). † Little ferrylhaemoglobin would be expected in the native preparation. These low values probably represent the inaccuracy in measuring the absorbance at the particular wavelengths used

	Saline	Intralipid	Thiopentone	Propofol	*P* (ANOVA)
%MetHb					
Hb alone	83.9 (1.5)	83.3 (1.6)	83.8 (1.5)	84.0 (1.5)	ns
$+H_2O_2$	24.3 (1.9)	23.1 (1.5)	21.6 (1.5)	22.8 (1.3)	ns
0 min	35.1 (2.1)	35.8 (2.6)	35.3 (2.3)	41.8 (2.5)	ns
10 min	45.0 (2.5)*	45.9 (2.6)*	46.4 (2.3)*	58.4 (2.6)	0.003
20 min	50.2 (2.3)**	52.3 (2.3)*	52.5 (2.1)*	64.0 (2.1)	0.0012
30 min	54.4 (2.3)**	55.2 (2.1)**	55.8 (2.0)*	67.8 (1.9)	0.0004
%FerrylHb					
Hb alone†	< 6	< 6	< 6	< 6	ns
$+H_2O_2$	31.5 (0.6)	32.1 (0.5)	32.7 (0.6)	32.8 (0.5)	ns
0 min	27.0 (0.9)	27.4 (0.9)	27.4 (0.8)	24.9 (0.9)	ns
10 min	23.6 (0.9)*	23.5 (0.9)*	23.1 (0.8)*	18.3 (1.0)	0.0011
20 min	21.7 (0.8)*	20.9 (0.8)*	20.7 (0.8)*	16.2 (0.8)	0.0003
30 min	19.9 (0.9)**	19.7 (0.7)**	19.3 (0.7)**	14.8 (0.7)	0.0002

In this study we have demonstrated that propofol, and to a lesser degree thiopentone, inhibited ABAP-induced haemolysis. Propofol (P-OH) is a phenol-based antioxidant and a potent inhibitor of lipid peroxidation *in vitro* [8, 9] and *in vivo* [18]. For example, it scavenges lipid peroxyl radicals ($LO_2\cdot$) through a process of hydrogen atom transfer to form a relatively stable propofol phenoxyl radical ($P\text{-}O\cdot$) and a lipid hydroperoxide (LOOH) (reaction 5) [8]:

$$P\text{–}OH + LO_2\cdot \rightarrow P\text{–}O\cdot + LOOH \qquad (5)$$

It is not clear if inhibition of ABAP-induced haemolysis by propofol resulted from scavenging of organic peroxyl radicals generated by ABAP (reaction 3), scavenging of lipid peroxyl radicals subsequently generated by it, or interruption of some other oxidant-mediated process initiated within, or close to, the cell membrane (e.g. generation of ferrylhaemoglobin species which have been shown to induce lipid peroxidation). Thiopentone has also been shown to inhibit lipid peroxidation *in vitro*, although the mechanisms for such an activity have not been defined.

Difficulties in explaining the inhibitory effects of propofol and thiopentone in this model result in part from the lack of information on the mechanisms of ABAP-induced haemolysis. It has been hypothesized that the release of iron from iron-containing proteins in tissues exposed to an oxidative stress may lead to a second wave of radical-mediated injury as a result of the ability of the released iron to catalyse further radical generation via the Haber–Weiss cycle (reactions 6–9) [1]:

$$Fe^{2+} + O_2 \rightarrow Fe^{3+} + O_2\cdot^- \qquad (6)$$

$$O_2\cdot^- + O_2\cdot^- + 2H^+ \rightarrow H_2O_2 + O_2 \qquad (7)$$

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \cdot OH \qquad (8)$$

$$O_2\cdot^- + Fe^{3+} \rightarrow Fe^{2+} + O_2 \qquad (9)$$

It is possible therefore that the release of haemoglobin during ABAP-induced haemolysis may contribute to subsequent erythrocyte membrane damage. Previous workers have dismissed this hypothesis because they could find no evidence for a change in the redox state of haemoglobin during this process [6]. In contrast, this study has shown that considerable methaemoglobin was formed during this process, although the demonstration that the concentrations were highest in the propofol-containing flasks (that is, the flasks in which haemolysis was delayed) does not ostensibly support the proposition that haem-bound iron contributes to erythrocyte oxidative injury.

The capacity of haem-containing proteins such as haemoglobin and myoglobin to generate radicals is thought to result in part from the ability of haem-bound iron to undergo one-electron transfer (oxidation–reduction) reactions and thereby oscillate between redox states (reaction 1). The absorption spectra of these haemoglobin species are distinct, allowing their relative proportions to be measured in both cellular and non-cellular preparations [13, 14]. How such redox transitions account for radical generation is not however entirely clear. It may result from the formation of the highly reactive hydroxyl radical via the Haber–Weiss cycle ($\cdot OH$, reactions 6–9), although several studies have demonstrated that such processes do not occur with intact haem proteins such as haemoglobin [1]. Other workers have suggested that haemoglobin and myoglobin may generate oxidant stress in tissues which is not mediated by the formation of $\cdot OH$ [13, 19], but which results from radical formation within amino acid residues of the globin element of the molecule (which can be represented by $-XH \rightarrow -X\cdot$). Thus, the oxidation of methaemoglobin ($HX\text{-}HbFe^{3+}$) by H_2O_2 and other hydroperoxides produces, via a two-electron transfer reaction, ferrylhaemoglobin ($\cdot X\text{-}HbFe^{4+}\text{-}OH$) [20] which is an unstable and reactive species in which the haem iron is one oxidizing equivalent above the met-state, with the second oxidizing equivalent present as a radical species on a protein residue within the globin moiety (as a tyrosine-derived phenoxyl radical):

$$\mathrm{HX\text{-}HbFe^{3+} + H_2O_2 \rightarrow \cdot X\text{-}HbFe^{4+}\text{-}OH + H_2O} \qquad (10)$$

Myoglobin behaves in a similar manner [21, 22] and in so doing promotes lipid peroxidation in cell membrane systems, although it is not clear if this is initiated by the protein radical or the ferrylhaem element of the molecule [12]. This injury can be attenuated by thiol-containing compounds such as *N*-acetylcysteine and *N*-(2-mercaptopropionyl)glycine [12]. Generation of ferrylhaemoglobin is also associated with increased concentrations of peroxidation in a ruptured erythrocyte preparation [23].

In order to explain the (higher) concentrations of methaemoglobin generated during ABAP-induced haemolysis in the presence of propofol we hypothesize that the organic hydroperoxide generated by ABAP (ROOH, reaction 4) oxidizes oxyhaemoglobin ($\mathrm{HX\text{-}HbFe^{2+}\text{-}O_2}$) to the ferryl state ($\mathrm{\cdot X\text{-}HbFe^{4+}\text{-}OH}$):

$$\mathrm{ROOH + HX\text{-}HbFe^{2+}\text{-}O_2 \rightarrow ROH + \cdot X\text{-}HbFe^{4+}\text{-}OH + O_2} \qquad (11)$$

in a manner analogous to the peroxidation by *hydrogen* peroxide (*H*OOH) described above (reaction 10). We suggest further that propofol (P–OH) reduces this ferryl species back to methaemoglobin thus:

$$\mathrm{P\text{–}OH + \cdot X\text{-}HbFe^{4+}\text{–}OH \rightarrow HX\text{–}HbFe^{4+} + {}^{-}OH + P\text{–}O\cdot} \qquad (12)$$

$$\mathrm{P\text{–}OH + HX\text{–}HbFe^{4+}\text{–}OH \rightarrow HX\text{–}HbFe^{3+} + P\text{–}O\cdot + H_2O} \qquad (13)$$

The formation of ferrylhaemoglobin during ABAP-induced haemolysis and reduced concentrations of this species in the propofol-containing flasks supports the first part of this hypothesis. The second series of experiments provided more definitive evidence that propofol, but not thiopentone, Intralipid or saline, promoted the reduction of ferrylhaemoglobin to methaemoglobin (reactions 12 and 13). It is not clear if generation of ferrylhaemoglobin is directly responsible for the oxidative stress to which erythrocytes are exposed when incubated with ABAP, although the association between reduced concentrations of ferrylhaemoglobin and lower rates of haemolysis in the propofol-containing flasks would support this contention.

We conclude from this *in vitro* study that propofol is capable of protecting erythrocytes against oxidant stress. Although this effect has been demonstrated at concentrations relevant to anaesthesia (12.5–50 μmol litre^{-1} is equivalent to 2.2–8.8 μg ml^{-1}), further work is required to demonstrate that this is a clinically significant effect. The mechanisms whereby propofol protects against ABAP-induced haemolysis remain to be fully elucidated. In this respect, although propofol inhibits lipid peroxidation, we have shown in these experiments that there is a further aspect to the antioxidant properties of this agent. Thus propofol can interact with high oxidation-state species of haemoglobin, and hence reduce ferrylhaemoglobin to the met-state. The reduction in the concentrations of these damaging high-oxidation state species may contribute to the protection afforded to membrane structures by the presence of this lipid-soluble radical scavenging molecule.

Acknowledgements

We are grateful to Zeneca for financial support for this study, and to Robert Atkinson, Philip Day, David Myers and Sheila Radford for technical assistance.

References

1. Halliwell B, Gutteridge JMC. Role of free radicals and catalytic metal ions in human disease: an overview. *Methods in Enzymology* 1990; **186**: 1–85.
2. Stocks J, Dormandy TL. The autoxidation of human red cell lipids induced by hydrogen peroxide. *British Journal of Haematology* 1971; **20**: 95–111.
3. Kellogg EW, Fridovich I. Liposome oxidation and erythrocyte lysis by enzymically generated superoxide and hydrogen peroxide. *Journal of Biological Chemistry* 1977; **252**: 6721–6728.
4. Niki E, Komuro E, Takahashi M, Urano S, Ito E, Terao K. Oxidative hemolysis of erythrocytes and its inhibition by free radical scavengers. *Journal of Biological Chemistry* 1988; **263**: 19809–19814.
5. Niki E. Free radical initiators as source of water- or lipid-soluble peroxyl radicals. *Methods in Enzymology* 1990; **186**: 100–108.
6. Miki M. Tamai H, Mino M, Yamamoto Y, Niki E. Free-radical chain oxidation of rat red blood cells by molecular oxygen and its inhibition by α-tocopherol. *Archives of Biochemistry and Biophysics* 1987; **258**: 373–380.
7. Giulivi C, Davies KJA. A novel antioxidant role for haemoglobin. The comproportionation of ferrylhaemoglobin with oxyhemoglobin. *Journal of Biological Chemistry* 1990; **265**: 19453–19460.
8. Murphy PG, Myers DS, Davies MJ, Webster NR, Jones JG. The antioxidant potential of propofol (2,6-diisopropylphenol). *British Journal of Anaesthesia* 1992; **68**: 613–618.
9. Musacchio E, Rizzoli V, Bianchi M, Bindoli A, Galzigna L. Antioxidant action of propofol on liver microsomes, mitochondria and brain synaptosomes in the rat. *Pharmacology and Toxicology* 1991; **69**: 75–77.
10. Aarts L, van der Hee R, Dekker I, de Jong J, Langemeijer H, Bast A. The widely used anesthetic agent propofol can replace α-tocopherol as an antioxidant. *FEBS Letters* 1995; **357**: 83–85.
11. Demopoulos HB, Flamm ES, Seligman ML, Jorgensen E, Ransohoff J. Antioxidant effects of barbiturates in model membranes undergoing free radical damage. *Acta Neurologica Scandinavica* 1977; **56**: 152–153.
12. Turner JJO, Rice-Evans CA, Davies MJ, Newman ESR. The formation of free radicals by cardiac myocytes under oxidative stress and the effects of electron-donating drugs. *Biochemical Journal* 1991; **277**: 833–837.
13. Winterbourn CC. Oxidative reactions of hemoglobin. *Methods in Enzymology* 1990; **186**: 265–273.
14. Berzofsky JA, Peisach J, Blumberg WE. Sulheme proteins. 1. Optical and magnetic properties of sulfmyoglobin and its derivatives. *Journal of Biological Chemistry* 1971; **246**: 3367–3377.
15. Armitage P, Berry G. *Statistical Methods in Medical Research*, 3rd Edn. Oxford: Blackwell Scientific Publications, 1994; 234.
16. Altman DG. *Practical Statistics in Medical Research*. London: Chapman and Hall, 1991; 212–213.
17. Sandhu IS, Ware K, Grisham MB. Peroxyl radical-mediated haemolysis: role of lipid, protein and sulfydryl oxidation. *Free Radical Research Communications* 1992; **16**: 111–122.
18. Murphy PG, Bennett JR, Myers DS, Davies MJ, Jones JG. The effect of propofol on free radical-induced lipid peroxidation in rat liver microsomes. *European Journal of Anaesthesiology* 1993; **10**: 261–266.

19. Puppo A, Halliwell B. Formation of hydroxyl radicals from hydrogen peroxide in the presence of iron. Is haemoglobin a biological Fenton reagent? *Biochemical Journal* 1988; **249**: 185–190.
20. McArthur KM, Davies MJ. Detection and reactions of the globin radical in haemoglobin. *Biochimica Biophysica Acta* 1993; **1202**: 173–181.
21. Davies MJ. Detection of myoglobin-derived radicals on reaction of metmyoglobin with hydrogen peroxide and other peroxidic compounds. *Free Radical Research Communications* 1990; **10**: 361–370.
22. Whitburn KD, Shieh JJ, Sellers RM, Hoffman MZ, Taub IA. Redox transformations in ferrimyoglobin induced by radiation-generated free radicals in aqueous solution. *Journal of Biological Chemistry* 1992; **257**: 1860–1869.
23. Paganga G, Rice-Evans C, Rule R, Leake D. The interaction between ruptured erythrocyte and low-density lipoproteins. *FEBS Letters* 1992; **303**: 154–158.

British Journal of Anaesthesia 1996; **76**: 544–551

Antinociceptive actions of intrathecal xylazine: interactions with spinal cord opioid pathways

C. S. GOODCHILD, Z. GUO, A. DAVIES AND J. P. GENT

Summary

We have studied rats with chronically implanted subarachnoid catheters. Xylazine, an α_2 adrenoceptor agonist, was injected intrathecally and nociceptive thresholds measured at two skin sites: the tail and the neck. Intrathecal xylazine (dose range 24.3–389 nmol) produced increases in electrical thresholds for nociception in the tail without any change in the neck; this observation suggested that the antinociceptive action of this drug was confined to the caudal part of the spinal cord responsible for tail innervation. The magnitude of this effect was dose-dependent. Tail flick latency also increased in these rats and the antinociceptive effects were antagonized in a dose-dependent manner by the selective α_2 adrenoceptor antagonist idazoxan (dose range 6.7–540 nmol). Intrathecal idazoxan also suppressed the increase in tail flick latency caused by the mu opioid agonist fentanyl (0.74 nmol) given intrathecally. This effect was also dose-dependent. The idazoxan dose–response curve for this suppression of fentanyl antinociception assessed with tail flick latency was the same as that for suppression of xylazine. In contrast, the antinociceptive effects of intrathecal xylazine were not affected by concurrent administration of opioid or $GABA_A$ antagonists. We conclude that intrathecal xylazine produced spinally mediated antinociceptive effects by combination with spinal cord α_2 adrenoceptors and that neither opioid nor GABA-containing propriospinal neurones were involved in the mediation of this effect. However, α_2 adrenoceptors in the spinal cord appear to be involved with antinociception produced by intrathecal fentanyl. (*Br. J. Anaesth.* 1996; **76**: 544–551)

Key words

Sympathetic nervous system, xylazine. Sympathetic nervous system, adrenergic block. Analgesics opioid, fentanyl. Spinal cord. Pain, mechanism.

Drugs selective for α_2 adrenoceptors and even subtypes of α_2 receptors have been shown to produce antinociceptive effects assessed with a variety of tests, such as hot plate, tail flick, paw pressure and visceral nociception [1–4]. Antinociceptive effects are readily demonstrated after intrathecal injection of these drugs. However, rarely is evidence provided that would indicate that the drug was confined in its action to the spinal cord and that it did not produce the antinociceptive effects by spreading to the brain.

It has been shown recently that differential or segmental antinociceptive effects occur after intrathecal injection of a variety of opioid and benzodiazepine agonists [5–9]. In experiments where segmental antinociceptive effects were clearly demonstrated with the electrical current threshold (ECT) test, increases in tail flick latency after some intrathecal drugs have also been shown [9–11]. In such experiments some of the antinociceptive effects of intrathecal 5-HT (increases in tail ECT but *not* tail flick latency) resulted from activation of µ opioid and $GABA_A$ systems within the spinal cord [11, 12]. A similar interaction between opioid and α_2 adrenoceptor spinal cord systems has been suggested, although proof of restriction of drug effects to the spinal cord, as described above, was not provided [13–15]. In this study, we report the segmental antinociceptive effects of an intrathecal α_2 adrenoceptor agonist and characterize these antinociceptive effects using ECT and tail flick latency tests. The combination of the drug with α_2 adrenoceptors was responsible for these effects and the possible involvement of spinal cord opioid or $GABA_A$ receptor systems was investigated.

Materials and methods

This work was carried out with permission from the licensing authorities in the UK (Home Office Licence No. PPL50-00131). In all experiments attention was paid to ethical guidelines for investigation of experimental pain in conscious animals [16]. Experiments were performed on male Wistar rats (weights 150–200 g) with chronically implanted lumbar subarachnoid catheters. Two tests, measurements of electrical current threshold for nociception (ECT) and tail flick latency, were used to demonstrate the antinociceptive effects of intrathecally administered α_2 adrenoceptor agonist (xylazine) and opioid agonists fentanyl (µ selective) and U50488H (κ selective). Dose–response relationships of xylazine

---

C. S. GOODCHILD*, MA, MB, BCHIR, PHD, FRCA, FANZCA, Z. GUO, MB, PHD (Department of Anaesthesia); A. DAVIES, BSC, J. P. GENT, MA, PHD (Department of Pharmacology); University of Leeds, Leeds LS2 9LN. Accepted for publication: October 27, 1995.

*Address for correspondence: Monash University Department of Anaesthesia, Monash Medical Centre, 246 Clayton Road, Clayton, Victoria, 3168 Australia.

given alone were assessed and then in a separate series of experiments, we investigated the effects of various antagonists on spinally mediated antinociception caused by a standard dose of intrathecal agonist. Dose–response curves for the opioids were determined in previous experiments [9]. Idazoxan (Research Biochemicals International; RBI) was used as the α_2 adrenoceptor antagonist, naloxone (Du Pont) as the opioid antagonist and bicuculline (Sigma, London) as the $GABA_A$ antagonist. All drugs were given intrathecally in a volume of 5 µl made up in physiological saline or 6% glucose solution.

CATHETER IMPLANTATION

Rats were anaesthetized with halothane in oxygen-enriched air ($F\text{I}_{\text{O}_2} = 0.5$) and a mid-lumbar laminectomy performed under aseptic surgical conditions using a 1.5-mm dental drill. The dura mater was exposed and incised. A catheter was manufactured from a 5-cm length of Portex tubing (i.d. 0.25 mm, o.d. 0.75 mm) stretched to a length of 10 cm in hot water (i.d. 0.1 mm approximately). It was introduced 1.0 cm into the subarachnoid space through an incision in the dura to lie next to the most caudal segments of the spinal cord, as described previously [9]. The catheter deadspace volume was measured before implantation; this varied between 4.5 and 7.5 µl. After closure of the surgical wounds with nylon and silk sutures (Ethilon and Mersilk; Ethicon Ltd) the animals were allowed to recover from general anaesthesia; this usually took 5–10 min.

After full recovery from general anaesthesia the animals were observed carefully for normal movement and behaviour. Any animal exhibiting signs of neurological damage was killed immediately (typically 5% of rats). The rest of the animals were subjected to a lignocaine test; we have previously found this to be a reliable test for correct intrathecal positioning of the catheter [8]. This test was performed after each cannulation and after each experiment in which intrathecal drug was administered. Thus intrathecal injection of drugs was confirmed. Any animal exhibiting a negative lignocaine test after cannulation (typically 10%) was excluded.

NOCICEPTIVE TESTS

A series of nociceptive tests was performed on each animal, the first on the day after cannulation. Although this is early after surgery, this preparation has been shown to produce stable baseline readings for the whole of the first week after cannulation [6, 9, 11, 17]. One test was performed each day on each animal up to a maximum of six. The rats were kept in groups of five before intrathecal cannulation and then in single boxes in rooms with a 12-h light–dark cycle. They were allowed free access to food and water throughout. They were placed individually in a proprietary restrainer and experiments were carried out in a quiet, darkened environment to minimize distraction of the animal by extraneous noise and light. Nociceptive thresholds were measured every 5 min using the ECT. In some experiments tail flick latency was also measured.

ELECTRICAL CURRENT THRESHOLD

Needle electrodes were placed 1 cm apart in the skin at the base of the neck. Wire electrodes were applied to the surface of the skin 1 cm and 5 cm from the base of the tail. The electrical current threshold (measured in mA at each skin site) was assessed, as described previously [9], every 5 min by the "up–down" method until three consecutive stable control readings had been obtained. The intrathecal drug or combination of drugs (see below) was then injected down the intrathecal catheter using the catheter swellings (used as markers to determine the catheter deadspace volume before implantation) to determine precisely the injection volume and dose. The electrical current threshold was measured at both skin sites every 5 min for at least another 20 min.

Individual responses were measured in mA. It has been found previously that these values for nociceptive thresholds vary between individuals and in the same individual at different times because of differences in electrode placement. They were therefore standardized by dividing the mean of the three threshold readings obtained 5, 10 and 15 min after intrathecal injection of agonist by the mean of the three corresponding readings taken before injection. This standardized response (denoted r) was a multiple of the control value.

TAIL FLICK LATENCY TEST

Tail flick latency was measured before assessment of ECT in the tail. The heat from a 150-W projector bulb was focused on to the tip of the tail painted black. Tail flick latency (measured in seconds) was assessed every 5 min until three stable control (pre-drug administration) measurements had been achieved (typically four trials), and then every 5 min after intrathecal drug administration. The increase in tail flick latency was standardized as a percentage of maximum possible effect (%MPE) calculated as follows:

$$\%\text{MPE} = \frac{\text{tail flick latency (post-drug)} - \text{tail flick latency (predrug)}}{\text{cut-off time} - \text{tail flick latency (pre-drug)}} \times 100$$

The cut-off time was the maximum time allowed for the animal to flick its tail away from the heat source before the lamp was automatically switched off. This was set at 10 s to avoid burning the tail.

ANTINOCICEPTIVE EFFECTS OF XYLAZINE

ECT was measured in the tail and neck in 48 experiments on 24 rats. In 30 of these experiments (11 rats) tail flick latency was also measured. Xylazine was injected intrathecally (24.3–389 nmol dissolved in 6% glucose 5 μl) over a period of 30 s with the animal tilted 45° head up to restrict distribution of the drug to the lumbar spinal cord. The standardized responses in both the neck and the tail were grouped for each dose of xylazine and the mean (SEM) calculated.

In nine of the above experiments xylazine 195 nmol was given intrathecally. The responses (ECT and tail flick latency) were standardized differently from those above to produce average time–response curves. The three control readings taken before intrathecal injection were averaged for ECT in the tail and neck. All values of current threshold (mA) at each 5-min period (whether before or after drug administration) were then divided by the corresponding average pre-injection value for that pair of electrodes. For tail flick latency each reading was standardized as %MPE using the equation above. The values thus obtained in different experiments for tail flick latency and ECT (tail and neck) were combined for each time of testing to produce means that were plotted on time–response curves. Thus the timing of onset of segmental antinociceptive effects (increases in tail ECT without any change in the neck threshold) could be compared with the onset of antinociceptive effect demonstrated by the tail flick latency test.

EXPERIMENTS USING IDAZOXAN

Xylazine

We performed 42 experiments in nine rats using tail flick latency and ECT tests. Intrathecal xylazine was given alone (195 nmol dissolved in 6% glucose 5 μl) at the beginning and after a series of once daily experiments with idazoxan in each rat. In intervening experiments (maximum of four) the same dose of xylazine was given intrathecally 5 min after a range of doses of idazoxan (6.7–540 nmol). The response of idazoxan was calculated as percentage suppression of the response to agonist given alone for both the ECT and tail flick latency tests. This was done by calculating the mean (R) of all tail responses to xylazine 195 nmol given alone for each test. Percentage suppression of control agonist response was calculated from the following equation:

$$\% \text{ suppression} = \frac{\text{R}-\text{r}}{\text{R}-1} \times 100\,\%$$

where R = response (either ECT (tail × control) or increase in tail flick latency, %MPE) in each individual experiment with antagonist. For the results of tail flick latency a value of 0, not 1, was used in the denominator. The results for percentage suppression by each dose of antagonist in individual experiments were grouped and the mean (SEM) calculated. These results were used to plot idazoxan dose–response curves.

Fentanyl

The experimental design in these experiments was the same as that for xylazine. Both nociceptive tests were used to assess the effect of intrathecal fentanyl 0.74 nmol dissolved in 6% glucose 5 μl. This dose was chosen from the dose–response relationship determined in previous experiments [9]. This dose caused segmental antinociceptive effects similar to those of xylazine. Sixty-five experiments were performed in 18 rats in which responses to agonist alone were assessed before and after an intervening series of experiments in which fentanyl 0.74 nmol was injected intrathecally 5 min after idazoxan (dose range 6.7–540 nmol), also injected intrathecally. We plotted percentage suppression of the antinociceptive effects of fentanyl by idazoxan, derived as above, and idazoxan dose–response curves.

Controls

Tail flick latency and ECT (tail) were measured every 5 min for 15 min before and 20 min after intrathecal injections of either idazoxan 180 or 540 nmol dissolved in 6% glucose 5 μl, or 6% glucose 5 μl alone in 13 rats. We searched for evidence of residual drug effects or progressive neurological damage at each time of testing by comparing the absolute values of ECT in the tail obtained at each time of testing with the first measurements obtained in that animal.

EXPERIMENTS USING NALOXONE

Xylazine

Sixteen experiments were performed in 11 rats. Both nociceptive tests were used to assess the effect of naloxone 2 mg kg^{-1} dissolved in saline 1 ml given i.p. on the antinociceptive effects of intrathecal xylazine 195 nmol dissolved in 6% glucose 5 μl. One experiment was performed on each animal per day. First the animal received intrathecal xylazine alone. On the following day, after three stable pre-injection readings had been obtained with both tests, naloxone was given i.p. 5 min before intrathecal injection of xylazine. Both nociceptive tests were carried out every 5 min for another 20 min. The results from each experiment were combined to produce mean (SEM) values for the responses in both tests to agonist alone and to agonist after i.p. injection of naloxone.

U-50488H

Larger doses of naloxone are required to suppress the effects of κ-selective compared with μ-selective opioids. U-50488H, a selective κ opioid agonist, was used to assess the effectiveness of the dose of naloxone to suppress all opioid responses in the xylazine experiments. The same design was used in these experiments as in those described above for fentanyl, xylazine and naloxone. We performed four experiments in four rats. Measurement of ECT (tail and neck) was used to assess the effects of intrathecal U-50488H on its own (210 nmol dissolved in saline 10 μl) and after i.p. naloxone 2 mg kg^{-1}. Tail flick latency was not used because the drug does not alter this measure of antinociception [7, 18, 19]. Results were expressed as mean (SEM) for U-50488H given alone and in the presence of naloxone.

STATISTICAL ANALYSIS

Comparisons of responses to xylazine, fentanyl and U-50488H were made with an unpaired *t* test to confirm that the doses used were equipotent. The effect of naloxone on the antinociceptive responses of xylazine and U-50488H was assessed using paired *t* tests.

EXPERIMENTS WITH BICUCULLINE

Eight experiments were performed on four rats in which measurements of both ECT and tail flick latency were used to assess the effects of the GABA$_A$ antagonist bicuculline on the antinociceptive action of intrathecal xylazine 195 nmol dissolved in 6% glucose 5 µl. A dose of 50 pmol of bicuculline was chosen from previous studies [6, 12]. In addition, intrathecal bicuculline 50 pmol given alone had no effect on the ECT in the tail [6]; these control experiments were therefore not repeated.

In another four rats the antinociceptive effects of intrathecal xylazine given alone and injected 5 min after administration of intrathecal bicuculline 50 pmol were assessed using both nociceptive tests. The responses in each group were combined to produce mean (SEM) values and compared using a paired *t* test.

Results

ANTINOCICEPTIVE EFFECTS OF INTRATHECAL XYLAZINE

Figure 1 shows the dose–response curve for the antinociceptive effects of intrathecal xylazine assessed with both nociceptive tests. Doses up to 389 nmol produced highly significant increases in the electrical current threshold in the tail (mean 2.67 (SEM 0.16) × control; $n = 8$; $P < 0.01$ paired Student's *t* test) with no significant increase in the electrical current threshold measured in the neck (1.1 (0.07); $n = 8$). At the same time intrathecal xylazine caused significant increases in tail flick latency (76 (10) %MPE; $n = 8$; $P < 0.01$ paired Student's *t* test).

Figure 2 shows time–response curves for tail flick latency and ECT responses in nine rats that received intrathecal xylazine 195 nmol. Intrathecal xylazine caused simultaneous significant increases in tail flick latency and ECT in the tail. These effects lasted for the duration of the experiment and were accompanied by no significant changes in electrical threshold in the neck. The time to offset of the responses could not be measured in this preparation because licensing restrictions only allowed restraint for this time. However, examination of control (predrug injection) and subsequent electrical current thresholds in the tail revealed no evidence for drug effects lasting until the next day or the occurrence of neurological damage; thresholds did not increase in any of the experimental series' as they progressed.

ANTAGONISM WITH INTRATHECAL IDAZOXAN

Xylazine

Doses of intrathecal idazoxan (6.7–540 nmol) given intrathecally 5 min before intrathecal xylazine 195 nmol caused dose-dependent suppression of the antinociceptive effects of xylazine assessed by both tests (fig. 3). There were no significant differences (paired Student's *t* test; $P > 0.5$) between the responses to xylazine given alone at the beginning of the series of experiments (ECT 2.05 (0.06) × control; tail flick latency 90.2 (5.5) %MPE) and those

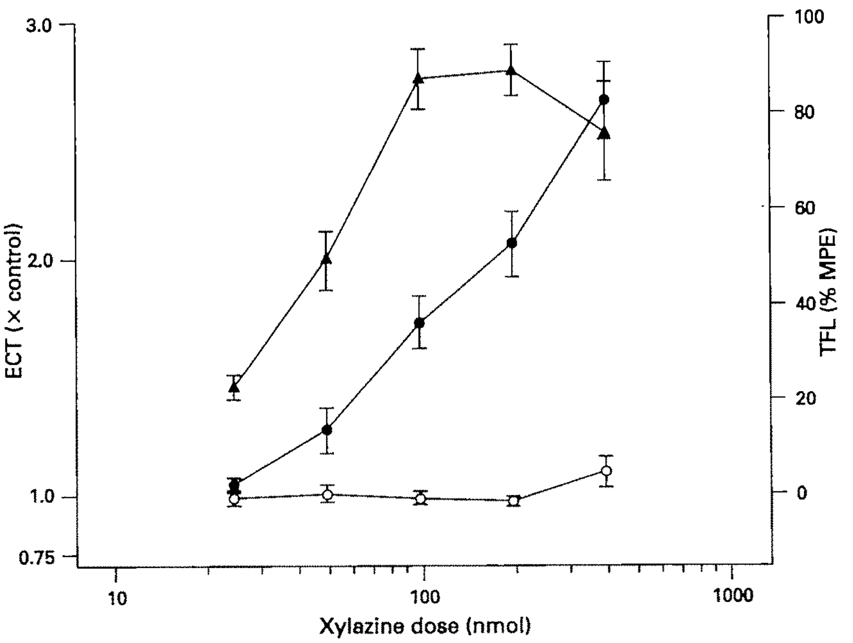


Figure 1 Intrathecal xylazine dose–response curves. Intrathecal xylazine caused dose-related antinociceptive effects demonstrated by an increase in tail flick latency (TFL (▲)) and increase in the electrical current threshold (ECT) in the tail (●) with no change in the neck (○) thresholds (mean, SEM). %MPE = percentage of maximum possible effect.

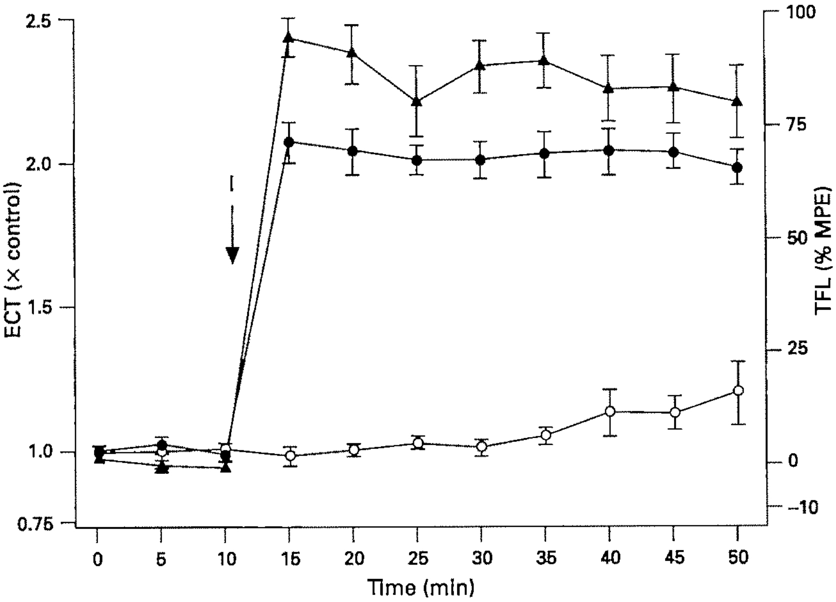


Figure 2 Time–response curves for intrathecal xylazine 195 nmol with the electrical current threshold test ((ECT) tail (●) and neck (○) electrodes) and tail flick latency (TFL) (▲) (mean, SEM) ($n = 9$). %MPE = percentage of maximum possible effect.

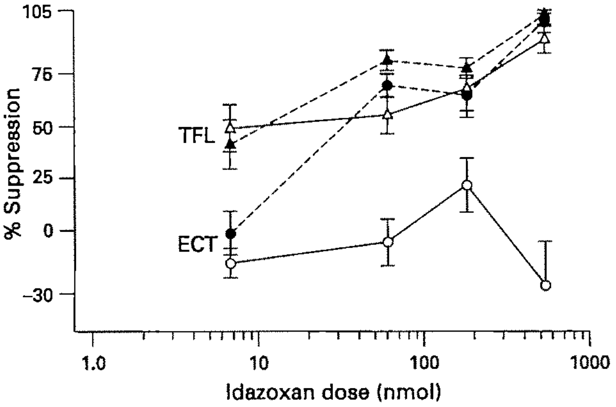


Figure 3 Idazoxan dose–response curves for suppression of the antinociceptive effects of xylazine (——) and fentanyl (——). Idazoxan suppressed the antinociceptive effects of xylazine in both nociceptive tests (tail flick latency (TFL) and electrical current threshold test (ECT)) but only suppressed the TFL effect of fentanyl.

obtained after the series of experiments (ECT 2.2 (0.11) × control; tail flick latency 94.8 (4.9) %MPE).

Fentanyl

The antinociceptive effects of fentanyl assessed with the tail flick latency test were suppressed by idazoxan, with the same dose–response relationship as that for suppression of the antinociceptive effects of xylazine assessed by both nociceptive tests (fig. 3). However, the effects of fentanyl assessed by the ECT test were not suppressed by idazoxan. There were no significant differences between the antinociceptive responses to intrathecal fentanyl given alone at the beginning of the series of experiments (ECT 1.93 (0.1) × control; tail flick latency 73.2 (5.9) %MPE) or after the series of experiments (ECT 2.18 (0.12) × control; tail flick latency 79.9 (4.7) %MPE). There were no significant increases in neck ECT (1.08 (0.11) × control). These responses also did not differ significantly from the corresponding responses to intrathecal xylazine given alone. The doses of the two drugs were therefore equieffective in the production of antinociceptive effects assessed by both tests, and the actions of both and interactions with idazoxan were restricted to the spinal cord. Control (pre-injection) and subsequent responses indicated that there was no drug accumulation or progressive neurological deficit as the experimental series progressed.

Both doses of idazoxan and 6% glucose did not cause significant changes in thresholds assessed by either nociceptive test (table 1).

EXPERIMENTS WITH NALOXONE

The dose of naloxone used (2 mg kg^{-1} i.p.) was sufficient to suppress totally the segmental antinociceptive effects produced by U-50488H, confirming previous studies with κ selective opioids [7, 17]. This high dose of naloxone did not produce any significant suppression of the antinociceptive effects caused by intrathecal xylazine (table 2). There were no significant differences between the responses to intrathecal xylazine and U-50488H given alone. All the responses to intrathecal U-50488H were segmental; no significant increases in neck ECT occurred (0.95 (0.11) × control).

EXPERIMENTS WITH BICUCULLINE

Intrathecal xylazine alone (195 nmol) produced significant segmental antinociceptive effects in the ECT test (1.96 (0.1) in the tail and 0.99 (0.01) in the neck; $n = 4$) and significant increases in tail flick latency (83 (17) %MPE; $n = 4$). Concurrent intrathecal administration of bicuculline 50 pmol did not significantly suppress either the ECT response (2.17 (0.1) in the tail and 1.0 (0.02) in the neck; $n = 4$) or tail flick latency (82.5 (13) %MPE; $n = 4$).

Table 1 Antinociceptive effects of idazoxan and 6% glucose (mean (SEM) (*n*)), as assessed by the electrical current threshold for nociception (ECT) and tail flick latency (TFL). %MPE = percentage of maximum possible effect

	ECT (× control)		
Controls	Tail electrodes	Neck electrodes	TFL (%MPE)
6% Glucose 10 μl	0.99 (0.03) (10)	1.01 (0.02) (10)	0.8 (1.0) (4)
Idazoxan 180 nmol	1.02 (0.03) (7)	0.98 (0.02) (7)	−1.3 (1.7) (7)
Idazoxan 540 nmol	0.95 (0.09) (7)	0.97 (0.04) (7)	−8.3 (3.2) (7)

Table 2 Effects of naloxone on the antinociceptive effects of U-50488H and xylazine, as assessed by the tail electrical current threshold for nociception (ECT) and tail flick latency (TFL)

	ECT (× control)				TFL	
	U-50488H alone	U-50688H + naloxone	Xylazine alone	Xylazine + naloxone	Xylazine alone	Xylazine + naloxone
Mean	2.04	1.01	2.25	1.97	86.5	85.3
SEM	0.13	0.05	0.20	0.07	8.84	9.26
n	4	4	16	16	16	16

Discussion

Intrathecal injections of xylazine produced segmental antinociceptive effects in the ECT test and simultaneously caused increases in tail flick latency. These effects occurred without any signs of sedation. The antinociceptive effects of xylazine assessed by both tests exhibited the same pattern of onset and were maintained for the entire experiment. Xylazine antinociception was maintained for much longer periods than any of the opioids or benzodiazepines in this preparation [7, 9]. The drug effects had disappeared 24 h later because there was no increase in control (pre-drug) tail electrical thresholds in subsequent experiments. These experiments have confirmed the antinociceptive effects of spinal α_2 adrenoceptor agonists reported by many others [1–4, 20–23]. Although most of those studies did not perform any of the manoeuvres mentioned above to prove a spinal cord action of the drug administered, the weight of evidence indicates a spinal site is responsible for the antinociception in a wide variety of tests. Waterman, Livingston and Bouchenafa showed segmental antinociceptive effects (five dermatomes around the catheter site) after spinal administration of xylazine in conscious sheep [22]; this effect was reversed completely by idazoxan. Our experiments allowed precise measurements of electrical thresholds and comparisons of dose–response curves to analyse drug interactions at the level of the spinal cord.

The dose–response curve for the tail flick latency response lies significantly to the left of that for the electrical current threshold response. Similar observations were made by Skingle, Hayes and Tyers [24] using clonidine, although they did not show differential responses in skin areas innervated by caudal compared with rostral spinal cord segments (a segmental effect). We have reported such differences in the dose–response curves for the two tests after intrathecal 5-HT [11].

Differences in the mechanisms responsible for the antinociception caused by 5-HT in tail flick latency compared with the ECT have also been demonstrated. The antinociceptive effects of 5-HT assessed by ECT could be suppressed by naloxone and bicuculline. However, the antinociceptive effects of 5-HT assessed by tail flick latency were not affected by either antagonist [11, 12]. Therefore, these results indicated involvement of propriospinal systems using GABA_A and μ opioid receptors in the pathways excited by ECT.

In the present study we have demonstrated that the antinociceptive effects of intrathecal xylazine are mediated by a combination of the agonist with spinal cord α_2 adrenoceptors because both the tail flick latency response and ECT were suppressed selectively by intrathecal idazoxan. This confirms the findings of Waterman, Livingston and Bouchenafa, although they did not perform a detailed dose–response analysis of the antagonism [22]. The same dose of idazoxan produced similar suppression of both responses. In contrast with the results obtained previously for intrathecal 5-HT [11, 12] it was not possible to demonstrate involvement of either an opioid or GABA_A receptor-mediated intermediate stage in the antinociception produced by xylazine; neither naloxone nor bicuculline suppressed increases in tail flick latency or ECT caused by intrathecal xylazine. The dose of naloxone used was sufficient to block all spinal opioid receptors as it was capable of completely suppressing the antinociceptive effects of the κ selective opioid against U-50488H in this series of experiments and has previously been shown to be capable of suppressing spinal antinociception caused by a variety of opioids and benzodiazepines [7, 17]. The dose of bicuculline used was also sufficient to block spinal GABA_A receptors as it has been shown previously to be effective in the suppression of spinally mediated antinociceptive effects of midazolam and 5-HT [12].

As segmental effects were demonstrated in all of our experiments for all intrathecal agonists it must be concluded that the actions of the agonists and their interactions with the antagonists must have occurred at the spinal cord level. We conclude therefore that the antinociceptive effects of xylazine result from an action on spinal α_2 adrenoceptors;

neither opioid nor GABA–benzodiazepine systems are involved as neither naloxone nor bicuculline suppressed these effects of xylazine.

Moreover, some of the spinally mediated antinociceptive effects of intrathecal fentanyl (ECT effects) result from actions at native μ opioid receptors and do not involve any other propriospinal system. In contrast, for increases in tail flick latency caused by intrathecal fentanyl there seems to be an interaction between the native μ opioid pathway and those pathways activated by α_2 adrenoceptor agonists, as the selective α_2 adrenoceptor antagonist idazoxan suppressed the effects of intrathecal fentanyl on tail flick latency. The results of these experiments with fentanyl and idazoxan indicate that the μ selective opioid binds with opioid receptors leading to activation of a spinal cord pathway that involves a native α_2 adrenoceptor; this is an essential part in the production of an increase in tail flick latency.

Interactions between μ opioid and α_2 adrenoceptor systems have been reported by several authors. For example, potentiation of the antinociceptive effects of intrathecal morphine by oxymetazoline has been reported [14]. Paw pressure and tail flick latency measurements were used but no proof of confinement of drug actions to the spinal cord was given. The potentiation (not simply the addition of effects) might therefore have been because of the actions of either or both drugs at supraspinal and spinal sites. The results presented in this study indicate that some potentiation is possible because the pathways activated by fentanyl and xylazine were not totally convergent. A similar relationship between the adrenoceptor and opioid systems has been reported from cross tolerance studies [13, 15, 25]. In one of these studies [25] it was shown that rats tolerant to ST-91 (an α_2 adrenoceptor agonist) showed no cross tolerance to morphine but morphine-tolerant rats demonstrated cross tolerance to ST-91. This might be predicted by the results of this study; induction of tolerance at the α_2 adrenoceptor by ST-91 also reduces the effect of morphine which acts via the adrenoceptor after binding with the opioid receptor. The nociceptive test used in this latter study was the tail flick latency test, the test which revealed convergence of the two spinal cord systems in the experiments reported here. Both of the other studies also used tail flick latency [13, 15] although one [13] also used paw pressure; neither study provided proof of confinement of the drugs to the spinal cord. Both of these latter studies seem to be at variance with the results reported here. The first [15] reported that chronic administration of clonidine (α_2 adrenoceptor agonist) decreased the antinociceptive effect of intrathecal morphine as tolerance to morphine developed, a result that would be predicted by the present study. However, they [15], in common with the second group of investigators [13], showed that chronic administration of morphine to cause morphine tolerance also decreased the effect of intrathecal α_2 adrenoceptor agonist. It is likely that morphine acted at sites in the brain leading to continuous activity in descending systems releasing noradrenaline onto spinal cord α_2 adrenoceptors [21, 26, 27]. This might have induced down-regulation of these receptors thereby inducing cross tolerance with the α_2 adrenoceptor agonists.

Acknowledgement

The authors thank Upjohn Ltd for a sample of U-50488H.

References

1. Danzebrink RM, Gebhart GF. Antinociceptive effects of intrathecal adrenoceptor agonists in a rat model of visceral nociception. *Journal of Pharmacology and Experimental Therapeutics* 1990; **253**: 698–705.
2. Sherman S, Loomis C, Milne B, Cervenko F. Prolonged spinal analgesia in the rat with the alpha-adrenoceptor agonist oxymetazoline. *European Journal of Pharmacology* 1987; **140**: 25–32.
3. Takano Y, Takano M, Yaksh TL. The effect of intrathecally administered imiloxan and WB4101: Possible role of α_2-adrenoceptor subtypes in the spinal cord. *European Journal of Pharmacology* 1992; **219**: 465–468.
4. Takano Y, Yaksh TL. Characterization of the pharmacology of intrathecally administered alpha-2 agonists and antagonists in rats. *Journal of Pharmacology and Experimental Therapeutics* 1992; **261**: 764–772.
5. Boulter N, Serrao JM, Gent JP, Goodchild CS. Spinally mediated antinociception after intrathecal chlordiazepoxide—further evidence for a benzodiazepine spinal analgesic effect. *European Journal of Anaesthesiology* 1991; **8**: 407–411.
6. Edwards M, Serrao JM, Gent JP, Goodchild CS. On the mechanism by which midazolam causes spinally mediated analgesia. *Anesthesiology* 1990; **73**: 273–277.
7. Goodchild CS, Sanghera S, Serrao JM, Gent JP. Analgesia mediated by spinal k-opioid receptors. *European Journal of Anaesthesiology* 1991; **8**: 227–231.
8. Goodchild CS, Serrao JM. Intrathecal midazolam in the rat: evidence for spinally-mediated analgesia. *British Journal of Anaesthesia* 1987; **59**: 1563–1570.
9. Serrao JM, Stubbs SC, Goodchild CS, Gent JP. Intrathecal midazolam and fentanyl in the rat: evidence for different spinal antinociceptive effects (published erratum appears in *Anesthesiology* 1989; 71: 482). *Anesthesiology* 1989; **70**: 780–786.
10. Goodchild CS, Guo Z, Gent JP. Spinally-mediated antinociceptive effects of xylazine, an alpha adrenoceptor agonist: interaction with spinal cord opioid pathways. *British Journal of Anaesthesia* 1991; **67**: 201P.
11. Guo Z, Gent JP, Goodchild CS. Intrathecal 5-hydroxytryptamine produces analgesia by activating spinal cord opioid pathways. *Pain* 1990; (Suppl 5): S103.
12. Guo Z, Gent JP, Goodchild CS. Two GABA mechanisms for spinally-mediated antinociception: evidence from antagonism of 5-hydroxytryptamine (5HT) by bicuculline. *British Journal of Anaesthesia* 1990; **64**: 589–590P.
13. Sherman SE, Loomis CW, Milne B, Cervenko FW. Tolerance to intrathecal oxymetazoline-induced analgesia, with paradigm-dependent cross-tolerance to intrathecal morphine. *Journal of Pharmacology and Experimental Therapeutics* 1988; **245**: 319–326.
14. Sherman SE, Loomis CW, Milne B, Cervenko FW. Intrathecal oxymetazoline produces analgesia via spinal alpha-adrenoceptors and potentiates spinal morphine (published erratum appears in *European Journal of Pharmacology* 1988; **154**: 345–348). *European Journal of Pharmacology* 1988; **148**: 371–380.
15. Solomon RE, Gebhart GF. Intrathecal morphine and clonidine: antinociceptive tolerance and cross-tolerance and effects on arterial pressure. *Journal of Pharmacology and Experimental Therapeutics* 1988; **245**: 444–454.
16. Zimmerman M. Ethical guidelines for investigation of experimental pain on conscious animals. *Pain* 1983; **16**: 109–110.
17. Serrao JM, Goodchild CS, Gent JP. Reversal by naloxone of spinal antinociceptive effects of fentanyl, ketocyclazocine, and midazolam. *European Journal of Anesthesiology* 1991; **8**: 401–406.
18. Schmauss C. Spinal kappa–opioid receptor-mediated antino-

ciception is stimulus-specific. *European Journal of Pharmacology* 1987; **137**: 197–205.

19. Schmauss C, Yaksh TL. In vivo studies on spinal opiate receptor systems mediating antinociception. II. Pharmacological profiles suggesting a differential association of mu, delta and kappa receptors with visceral chemical and cutaneous thermal stimuli in the rat. *Journal of Pharmacology and Experimental Therapeutics* 1984; **228**: 1–12.
20. Reddy SV, Maderdrut JL, Yaksh TL. Spinal cord pharmacology of adrenergic agonist-mediated antinociception. *Journal of Pharmacology and Experimental Therapeutics* 1980; **213**: 525–533.
21. Reddy SV, Yaksh TL. Spinal noradrenergic terminal system mediates antinociception. *Brain Research* 1980; **189**: 391–401.
22. Waterman A, Livingston A, Bouchenafa O. Analgesic effects of intrathecally-applied alpha 2-adrenoceptor agonists in conscious, unrestrained sheep. *Neuropharmacology* 1988; **27**: 213–216.
23. Yaksh TL, Reddy SV. Studies in the primate on the analgesic effects associated with intrathecal actions of opiates, alpha-adrenergic agonists and baclofen. *Anesthesiology* 1981; **54**: 451–467.
24. Skingle M, Hayes AG, Tyers MB. Antinociceptive activity of clonidine in the mouse, rat and dog. *Life Sciences* 1982; **31**: 1123–1132.
25. Stevens CW, Monasky MS, Yaksh TL. Spinal infusion of opiate and alpha-2 agonists in rats: tolerance and cross-tolerance studies. *Journal of Pharmacology and Experimental Therapeutics* 1988; **244**: 63–70.
26. Shiomi H, Takagi H. Morphine analgesia and the bulbospinal noradrenergic system: increase in the concentration of normetanephrine in the spinal cord of the rat caused by analgesics. *British Journal of Pharmacology* 1974; **52**: 519–526.
27. Takagi H, Shiomi H, Kuraishi Y, Fukui K, Ueda H. Pain and the bulbospinal noradrenergic system: pain-induced increase in normetanephrine content in the spinal cord and its modification by morphine. *European Journal of Pharmacology* 1979; **54**: 99–107.

British Journal of Anaesthesia 1996; **76**: 552–559

REVIEW ARTICLE

Postoperative sleep disturbances: mechanisms and clinical implications

S. ROSENBERG-ADAMSEN, H. KEHLET, C. DODDS AND J. ROSENBERG

Major surgery is beset by complications such as pulmonary, cardiac, thromboembolic and cerebral dysfunction, which cannot be attributed solely to inadequate surgical and anaesthetic techniques, but rather to increased organ demands caused by the endocrine metabolic response to surgical trauma [33]. Postoperative cerebral dysfunction comprises delirium, confusion and milder degrees of mental dysfunction [1, 48, 53, 62], and disturbances in the normal sleep pattern [4, 7, 9, 13, 17, 34, 39, 42, 65]. Changes in early postoperative sleep [4, 7, 8, 13, 17, 34, 39, 42, 65] and sleep after non-surgical stress [10, 20, 24, 26, 27, 29, 60] are characterized by a decrease in total sleep time, elimination of rapid eye movement (REM) sleep, a marked reduction in the amount of slow wave sleep (SWS) and increased amounts of non-REM (N-REM) sleep stage 2. Recent data have suggested that postoperative sleep disturbances may be involved in the development of altered mental function [27], postoperative episodic hypoxaemia [38, 65] and haemodynamic instability [40]. The aim of this article, therefore, is to review the incidence and duration of postoperative sleep disturbances, and to evaluate possible mechanisms and potential implications for postoperative outcome.

The normal sleep pattern

Using standardized polysomnographic recordings, which include simultaneous electroencephalographic (EEG), electro-oculographic (EOG) and electromyographic (EMG) recordings, sleep can be divided into different sleep stages (see below). By questionnaire, subjective sleep quality, which has been shown to be related to total sleep duration and number of awakenings [3], may be assessed.

Sleep is not homogeneous, but is divided into two discrete forms, REM and N-REM, by their electrophysiological characteristics [58], and each has been subdivided further. There are striking differences between these two sleep patterns. For example, arousal to effective awareness depends on the magnitude of the stimulating input and the "depth" of the sleep stage. Wakening from REM and stage 4 N-REM requires the greatest input, and this is as true for external stimuli, such as noise and light, as for internal autonomic signals, such as hypoxia or pulmonary stretch receptor reflexes. This clearly has an important influence on the hazards that may accompany deep sleep after surgery (see below).

N-REM sleep is subdivided into four stages of increasing depth or resistance to arousal, with stage 1 N-REM being light sleep and stage 4 N-REM very deep sleep (fig. 1). The physiology of N-REM sleep is based entirely on the autonomic medullary and brain stem control systems. There is a reduction in basal metabolic rate and this is associated with a progressive decrease in oxygen requirement, heart rate, arterial pressure, temperature and ventilation. The decrease in arterial pressure is largely because of peripheral vasodilatation, with cardiac output remaining relatively unchanged. Other physiological variables are generally unchanged during N-REM sleep. The tone of the anti-gravity muscles decreases with increasing depth of N-REM sleep, but the tonic drive to the diaphragm is maintained at all levels and types of sleep. There is a reduction in hypoxic and hypercapnic ventilatory responses and the response to increasing respiratory resistive loads. The maximum decrease occurs in stages 3 and 4 N-REM (also called slow wave sleep (SWS)), where for example the hypoxic drive decreases by 40%.

REM sleep is the phase most closely associated with dreaming. It is more akin to full awareness than sleep, in the variability and rapidity of changes in physiological state. There are marked variations in arterial pressure and heart rate, rate and depth of breathing, and metabolic rate. It appears that we act out our dreams physiologically. Major differences from N-REM sleep are also evident in respiratory control during REM sleep. The α-motor neurones are hyperpolarized during REM, with the exception of the facial muscle supply and that of the diaphragm. The hypoxic ventilatory response is reduced by up to 60% and carbon dioxide responses to between 27%

(*Br. J. Anaesth.* 1996; **76**: 552–559)

Key words
Sleep. Sleep, postoperative. Hypoxaemia.

SUSAN ROSENBERG-ADAMSEN, MD, HENRIK KEHLET, MD, PHD, CHRIS DODDS, MB, BS, MRCGP, FRCA, JACOB ROSENBERG*, MD, DMSC, Department of Surgical Gastroenterology 235, Hvidovre University Hospital, DK-2650 Hvidovre, Denmark, Department of Anaesthesia, South Cleveland Hospital, Cleveland TS4 3BW, England.

*Address for correspondence: Department of Surgical Gastroenterology 235, Hvidovre University Hospital, DK-2650 Hvidovre, Denmark.

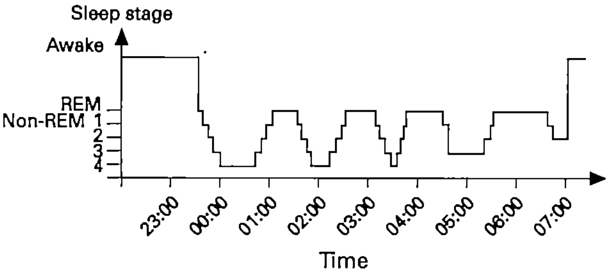


Figure 1 The normal sleep pattern (hypnogram).

and 0% [15] of the awake response. The arousal response to hypoxia requires a decrease in Sp_{O_2} to less than 70% for activation.

Sleep is essential and any alteration or suppression of specific sleep stages results in a rebound response when the inhibition is removed. The harmful effects of prolonged REM sleep in the postoperative period have been well documented. The time scale for these changes has not been described fully but they are thought to last for 1 or more weeks after surgery.

The mechanisms underlying the initiation and maintenance of sleep and its stages are still speculative, but there are some important features related to the effects of surgery and anaesthesia on sleep. N-REM sleep is linked closely with the central action of serotonin (5-HT) and, to a lesser degree, the monoamine noradrenaline. There are marked reductions in the amount of deep N-REM sleep in patients given benzodiazepines and opioids. REM sleep can be initiated by acetylcholine agonists in animal studies and neostigmine in human volunteers. Atropine markedly reduces REM sleep. Also α_2 agonists such as clonidine, or dopamine (D_2) agonists such as apomorphine, reduce REM sleep, and the monoamine oxidase inhibitors (MAOI) can almost abolish REM. Prazosin, an α_1 antagonist, increases the incidence of cataplexy, a REM-related component of narcolepsy. It is tempting to try to isolate key drugs as causal agents, for instance opioids, but the same pattern is seen after regional anaesthesia alone (see below).

Airway control during sleep

During wakefulness, the airway is maintained patent by the action of the paired strap muscles surrounding the oropharynx and pharyngopharynx. This prevents the collapse of this part of the airway by the subatmospheric pressures generated by the chest and diaphragmatic action. On initiation of sleep there is a progressive decrease in upper airway muscle tone and maintenance of the normal action of the chest and diaphragm. In the light stages of N-REM sleep this disproportionate decrease in tone makes collapse more likely. As the airway becomes progressively narrow, airflow becomes suddenly turbulent. This produces vibration of the upper airway or snoring. Thus snoring is partial airway obstruction. If there is a greater load on the airway muscles because of fatty deposits (obesity) or increased inspiratory resistance (such as the macroglossia of Down's syndrome), further collapse is likely and may culminate in complete airway obstruction.

In REM sleep, atonia of the anti-gravity muscles predisposes to instability of the airway, and most obstructive apnoea episodes occur in this stage of sleep. When the airway has become obstructed, further inspiratory effort is futile because of the lack of muscle tone during deep sleep. Vigorous paradoxical ventilatory movements are easily visible but ineffective. The only route to recovery of the airway is arousal from sleep which is usually very brief (< 5 s) and not associated with recall. The cycle of sleep–obstruction / hypoxia–arousal–sleep–obstruction/hypoxia may occur more than 100 times each hour. The consequences of these episodes of obstruction are two-fold: physiological effects of the progressive hypoxia and hypercapnia, and daytime sleepiness from repeated life-saving arousals. These patients are described as suffering from obstructive sleep apnoea (OSA) syndrome [46].

The consequences of airway obstruction during sleep may be profound and include progressive hypoxia, bradycardia and hypercapnia. Pulmonary artery pressure increases by hypoxic pulmonary vasoconstriction, and there is a generalized increase in systemic peripheral resistance. During REM sleep this causes increased oxygen demands at a time when hypoxia and hypertension are marked and ischaemic injury becomes likely, particularly of the heart. If apnoeas occur during N-REM, the association of hypotension and hypoxia may lead to cerebral hypoperfusion and stroke.

Function of sleep

The function of sleep is largely unknown, although several theories have been proposed. The most widely held theory is that sleep serves as a period of restoration, either total body or neurological restoration [66]. Total or selective sleep deprivation affects particularly the brain, with psychological and neurological dysfunction [30], impairment in behavioural and psychological performance [8, 23, 30] and sleepiness [8], and impaired concentration [30] and performance on psychometric tests [8, 23, 30]. Finally, mood is affected, with increased sadness and irritability, and decreased vigour [30]. Selective REM sleep deprivation produces a state of pronounced irritability and lability, and signs of confusion, anxiety and suspicion [2]. Deprivation of REM sleep is followed by a significant increase (rebound) in a recovery night [2]. SWS deprivation produces a feeling of physical discomfort [2], characterized by a depressive and hypochondrial reaction [2]. Selective deprivation of SWS also produces a rebound in SWS during a recovery night [2, 23].

The postoperative sleep pattern

Only six studies have been performed with EEG recording of sleep in postoperative patients after non-cardiac surgery, including a total of 35 patients after major abdominal surgery [4, 17, 39, 65], 18 patients after herniorrhaphy [17, 34] and 46 patients after minor undefined surgery [42] (table 1).

Table 1 Summary of clinical studies with EEG measured sleep after non-cardiac surgery. ↑ = Increased, ↓ = decreased, → = unchanged, 0 = not measured

	Type of surgery	Postoperative nights	Total sleep time	Duration of REM sleep	Duration of SWS	Duration of stage 2	No. of arousals	Rhythmicity	No. of patients
Aurell & Elmqvist [4]	Major non-cardiac surgery	1–4	↓	↓	↓	↑	0	0	9
Ellis & Dudley [17]	Inguinal hernia repair	1, 2	↓ (in all)	↓	↓	↑	↑	↓	8
	Upper abdominal surgery	1, 2	↓ (in all)	↓	↓	↑	↑	↓	4
Knill and colleagues [39]	Cholecystectomy	1, 2, (3)	→	↓	↓	↑	↑	↓	6
		(3), 4, 5, 6	→	↑ (in all)	→	→	→	↓	
	Gastroplasty	1, 2, (3)	→	↓	↓	↑	↑	↓	6
		(3), 4, 5	→	↑ (in all)	→	→	→	↓	
Rosenberg and colleagues [65]	Major abdominal surgery	1, (2)	→	↓	↓	↑	→	0	10
		(2), 3	→	↑ (in 7 of 10)	↓ (in 8 of 10) ↑ (in 2 of 10)	→	→	0	
Kavey & Altshuler [34]	Herniorrhaphy	1, 2	↓	↓	↓ (entirely absent in 9 of 10)	↑	↑	→	10
		3, 4	→	→ (in 6 of 10) ↑ (in 4 of 10)	→ (in 6 of 10) ↓ (in 4 of 10)	→	↑	→	
Lehmkuhl and colleagues [42]	Minor surgery	1	→	↓	↓	↑	0	0	46

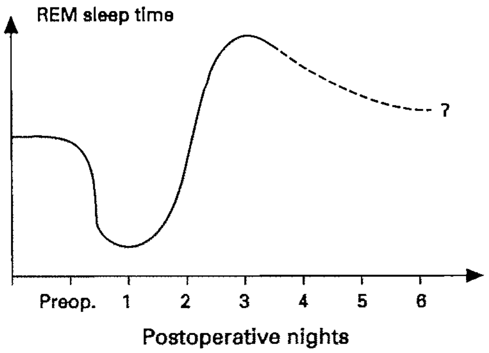


Figure 2 Changes in total REM sleep on pre- and postoperative nights (based on [4, 17, 34, 39, 42, 65]).

After abdominal surgery all patients were sleep deprived, as shown by total sleep time, proportion of REM sleep and SWS on the first and second postoperative nights in the ICU [4] and on the ward [17, 34, 38, 39, 65]. Total sleep time was reduced by up to 80% on at least 1 of the first postoperative nights [4, 7, 13, 17, 34], with considerable inter-individual variation. Throughout the operative night and the subsequent 1 or 2 nights, sleep was highly fragmented with numerous movement arousals and spontaneous awakenings with long wake periods [17, 34, 39], preventing the inherent rhythmicity of sleep and the normal distribution of sleep stages [17, 39].

REM sleep is usually absent on the first and sometimes the second and third postoperative nights [4, 17, 34, 38, 39, 42, 65]. During the following 2–4 nights, when other sleep abnormalities recover, REM sleep reappears with increased density and duration (rebound) in most patients [34, 38, 39, 65] (fig. 2). In patients undergoing cholecystectomy and gastroplasty, Knill and colleagues showed that increments in REM sleep during rebound were primarily a result of lengthening of individual REM sleep periods rather than to an increased number of periods [31]. Thus, increased total REM sleep time, combined with increased REM density, results in a substantial rebound in total REM activity [39]. The increase in REM activity is associated with frequent reports of distressing and vivid nightmares [39]. Nightmares have been shown to be frequent (about 20%) during the first week after major non-cardiac surgery [7, 9], with the highest incidence on the fourth postoperative night [9], corresponding to the period of rebound REM sleep.

On postoperative nights 1–4 there was a marked reduction in the amount of SWS [4, 17, 34, 39, 42, 65]. In one study SWS was absent in all 10 patients studied on the first and second nights after major abdominal surgery [65]. An increased duration of SWS (rebound) in the middle of the first post-operative week may occur after initial deprivation of SWS [65].

The duration of the abnormal postoperative sleep pattern has been described only poorly. No studies with EEG monitoring have been performed later than the sixth night after abdominal surgery. Total sleep time is gradually normalized to the pre-operative level within the first postoperative week [34]. REM sleep was still increased in nine of 12

Table 2 Summary of studies of postoperative sleep quality (measured by questionnaire). ↑ = Increased, ↓ = decreased, → = unchanged, 0 = not measured. *Patients were asked retrospectively about the whole postoperative period up to 2 yr after the surgical procedure

	Type of surgery	Postoperative nights	Total sleep time	No. of arousals/awakenings	Subjective sleep quality	Nightmares	No. of patients
Ellis & Dudley [17]	Inguinal hernia repair	1, 2	↓(in all)	↑(in all)	↓(in all)	0	8
	Upper abdominal surgery	1, 2	↓(in all)	↑(in all)	↓(in all)	0	4
Kavey & Altshuler [34]	Inguinal hernia repair	1, 2	↓	↑	↓	0	10
		3, 4	→	↑	↓	0	
Closs [13]	Abdominal surgery	3	↓	↑	↓	0	100
Beydon and colleagues [7]	Elective orthopaedic, abdominal and vascular surgery	1, 2	↓	0	↓	↑(in 23 %)	157
		15 days after discharge	0	0	↓(in 24 %)	0	
Brimacombe & Macfie [9]	Day surgery (not specified)	1–7	0	↑	↓(in 14 %)	↑(in 12 %)	57
	Elective cardiac surgery	1–7	0	↑	↓(in 55 %)	↑(in 289 %)	104
	Major non-cardiac surgery	1–7	0	↑	↓(in 30 %)	↑(in 19 %)	53
	Minor orthopaedic surgery	Retrospective*	0	0	0	↑(in 7 %)	57

patients on the sixth night after cholecystectomy or on the fifth night after gastroplasty [39]. In most patients SWS gradually returned towards normal during the third and fourth postoperative night [34, 39, 65].

Studies based on observations by staff have shown that during the first night in the intensive care unit (ICU), the majority of subjects (56 %) were sleep-deprived with respect to total sleep time [27]. Similarly, the subjective feeling of sleep quality in postoperative patients has been shown to be decreased markedly during the first 1 or 2 nights followed by recovery of sleep quality, for most patients before discharge [7, 13, 17, 34] (table 2). A questionnaire study showed that approximately 23 % of patients after elective orthopaedic, vascular or abdominal surgery had decreased sleep quality at the time of discharge from hospital, and about 25 % of these patients showed changes for more than 2 weeks after discharge [7].

In summary, profound alterations in sleep pattern occur during the first 1–6 nights after major abdominal surgery. As previous studies have concluded that sleep duration and the frequency and periodicity of sleep disruption are the most important determinants for the restorative capability of sleep [3, 8, 23], such sleep changes may be expected to influence restoration of body organ dysfunction and in particular cerebral function.

Pathogenesis of postoperative sleep disturbance

Several factors may contribute to the disturbed sleep pattern in the surgical patient (fig. 3). The magnitude of surgery is important, as the reduction in REM sleep, SWS and the lack of inherent rhythmicity are more pronounced after major (gastrectomy or vagotomy) than minor (hernia repair) surgery [17]. In questionnaire studies, the greatest incidence of sleep disturbances was also found after the more major surgical procedures [13, 17, 27]. The duration of the operative procedure was related to the duration of postoperative sleep disturbance [17], probably as a result of more extensive surgical trauma.

In studies of patients receiving general or regional anaesthesia for herniorrhaphy [34], minor orthopaedic procedures [9] or minor undefined surgery [42], a similar degree of sleep disturbance was found, regardless of anaesthetic technique, suggesting that general anaesthesia *per se* is not an important pathogenic factor. Furthermore, general anaesthesia of 3 h duration in non-surgical volunteers produced only a modest reduction in SWS for 1 night and no changes in REM sleep [51]. Furthermore, similar changes in sleep pattern as are seen in postoperative patients have been found in non-surgical patients with acute ischaemic stroke [24], acute myocardial infarction [10], congestive heart failure [26] and medical and trauma ICU patients [20, 29, 60]. Thus general anaesthesia *per se* must be of minor importance in the pathogenesis of postoperative sleep disturbance, compared with the physical stress response caused by the surgical trauma.

The injury of surgery is followed by a complex

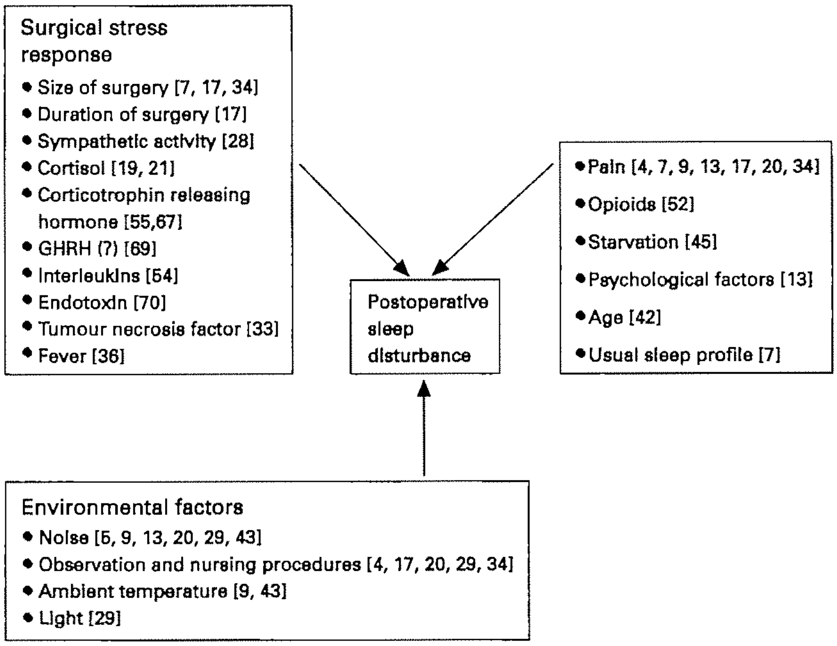

Surgical stress response
• Size of surgery [7, 17, 34]
• Duration of surgery [17]
• Sympathetic activity [28]
• Cortisol [19, 21]
• Corticotrophin releasing hormone [55,67]
• GHRH (?) [69]
• Interleukins [54]
• Endotoxin [70]
• Tumour necrosis factor [33]
• Fever [36]
Postoperative sleep disturbance
•Pain [4, 7, 9, 13, 17, 20, 34]
•Opioids [52]
•Starvation [45]
•Psychological factors [13]
•Age [42]
•Usual sleep profile [7]
Environmental factors
• Noise [5, 9, 13, 20, 29, 43]
• Observation and nursing procedures [4, 17, 20, 29, 34]
• Ambient temperature [9, 43]
• Light [29]

Figure 3 Factors which may contribute to postoperative sleep disturbances.

stress response involving hormones and humoral mediators of the endocrine–metabolic system, immunosuppression and an inflammatory response [6, 35]. The inflammatory reaction constitutes the local response, whereas endocrine–metabolic activation with increased plasma concentrations of catabolic hormones and reduced concentrations of anabolic hormones, leads to hypermetabolism with acceleration of most biochemical reactions, including muscle protein breakdown, resulting in a negative nitrogen balance [35]. The response may last for a few days or even weeks, depending on the magnitude of the surgical insult and occurrence of complications.

The increased postoperative sympathetic activity with increased catecholamines may contribute to postoperative sleep disturbances, as high levels of noradrenergic activity maintain wakefulness [28]. The postoperative influence of surgical trauma on insulin is biphasic, with an impaired insulin response to glucose during the initial phase followed by an increased insulin response but with concomitant increased peripheral insulin resistance (post-receptor defect) [35]. Cortisol, another of the key mediators in the endocrine response to surgery, causes reduction in REM sleep and increases non-REM sleep when administered to healthy volunteers [19, 21]. Furthermore, corticotrophin-releasing hormone, which is increased in surgical stress, decreases non-REM sleep and increases wakefulness in a dose-dependent manner in rabbits and rats [55, 67]. In contrast, growth hormone releasing hormone (GHRH) may have a sleep inducing effect [69], and is probably increased during the postoperative period.

Administration of one of the key mediators of injury, interleukin-1, into the lateral ventricle of rabbits results in hyperthermia and increased non-REM sleep, with suppression of REM sleep, thus resembling the postoperative situation [54]. Pretreatment with an interleukin-1 receptor antagonist prevented interleukin-1-induced sleep disturbances [54]. Endotoxin administration to healthy volunteers [70] and intracerebroventricular injection of tumour necrosis factor in rabbits [33] also caused deprivation of REM sleep and an increase in non-REM sleep, with no changes in SWS. As REM sleep is controlled by many regions in the brain and there is a dynamic interaction between cortex and other subcortical systems [32], the postoperative REM sleep disturbance may represent a global excitatory effect of the entire surgical stress response on the brain, rather than being caused by specific mediators of the surgical stress response.

Fever, which is seen commonly in postoperative patients, is associated with decreased REM sleep and increased SWS in rats with fungal infections [36]. It is not known if the fever-induced sleep disturbance is mediated by cytokines only or if it is induced by the increased temperature *per se*.

Morphine 0.1 and 0.2 mg kg^{-1} i.m., administered to healthy volunteers without pain, disrupted sleep in a dose-dependent manner [52]. After a dose of 0.1 mg kg^{-1}, only SWS was reduced, whereas a larger dose of 0.2 mg kg^{-1} produced a marked reduction in both REM sleep and SWS with an increase in nocturnal awakenings [52]. There are no data on the effect of systemic or extradural morphine on sleep in postoperative patients.

After operation, pain is the most commonly reported cause of night-time awakenings [13], and based on questionnaires, provision of analgesia is the most helpful intervention to improve sleep [13]. No comparisons have been made between opioid and non-opioid drugs. In patients with pain from active rheumatoid arthritis, sleep disturbances similar to the postoperative period have been demonstrated [49]. The role of pain *per se*, that is nociceptive stimulation *vs* concomitant release of inflammatory mediators (cytokines) and stress hormones, has not been evaluated.

The noise level in an ICU is usually greater than is internationally recommended at all times of the day and night [5]. Acoustically disturbed sleep has a decreased subjective quality, with less SWS than undisturbed sleep [23]. Patients have reported noise as one of the most disturbing factors of sleep in the postoperative period on the ward [7, 13] and in the ICU [29]. In addition, other "external" factors such as frequent observations and therapeutic procedures [29] and a high room temperature [43] may have a negative effect on sleep pattern in the surgical patient. An i.v. catheter did not affect sleep in volunteers [37], but starvation, as seen in most patients after major procedures, may be associated with decreased REM sleep and increased SWS, as shown in volunteers [45].

Obstructive sleep apnoea (OSA) syndrome

Special mention should be made of patients with the sleep apnoea syndrome. Sleep apnoea is defined as a pause of more than 10 s in breathing during sleep, and OSA is defined as at least five apnoeas per hour [48]. OSA is a common finding in non-surgical patients, with an incidence of 1–9% [48], although the more severe forms are less common. It has several major implications for anaesthesia and surgery throughout the operative period. These patients have repetitive episodes of often severe hypoxia and may have pulmonary hypertension. They may have impaired reflex responses to hypoxia, hypercapnia and inspiratory loads, and may also have altered autonomic cardiovascular reflexes [14, 71]. The treatment of OSA with nasal continuous positive airway pressure (CPAP) is highly effective at preserving the airway during sleep and over several weeks can improve the diminished reflex responses to hypoxia and hypercapnia [44]. However, it is more prudent to assume that they do not respond normally to any of these challenges during anaesthesia and in the postoperative period. They may be vulnerable to depressant medication such as benzodiazepines and opioids [12], and respiratory arrest can occur if these are given. All common anaesthetic induction agents, volatile and i.v., reduce upper airway tone in an identical manner to deep sleep. Some of the predisposing causes of sleep apnoea, such as a large tongue and recessive mandible, are also associated with difficulty in tracheal intubation and maintenance of a patent airway. Recovery from surgery and anaesthesia, while the normal protective reflexes are returning, may be a hazardous time, and obstruction of the airway can be difficult to overcome. This must be borne in mind after return to the ward if sedation or opioid analgesia is given. Regional methods of pain relief are believed to be safer than systemic opioid analgesia [18]. If patients are treated with CPAP, it is important that they bring their machines into hospital as they can be used in the recovery unit to preserve the airway until full recovery occurs and on the ward while their sleep returns to normal.

No data are available about postoperative sleep in patients with sleep apnoea syndrome, but extreme episodic oxygen desaturation in the late postoperative period has been described in a patient with the sleep apnoea syndrome [61], which may therefore be a potential surgical risk factor.

Clinical implications of postoperative sleep disturbances

The clinical consequences of suppression of REM sleep and SWS with subsequent rebound in the postoperative period remain unknown, although there are several potentially important implications.

The postoperative rebound of REM sleep in the middle of the first postoperative week may contribute to the development of sleep-disordered breathing and nocturnal hypoxaemia [38, 65]. Episodic hypoxaemia is more frequent during periods of REM rebound than during other sleep stages in the postoperative period [65].

REM sleep is associated with profound sympathetic activation on nights with postoperative rebound [41] and in normal subjects [46, 68]. REM sleep in normal subjects is associated with haemodynamic instability [40, 47, 68], and increased mean arterial pressure [47, 68]. In the postoperative period these haemodynamic changes may occur with the hypoxaemic episodes [38, 65], and following uncomplicated abdominal surgery, episodic hypoxaemia was associated with cardiac ischaemia [22, 59, 64]. Sleep apnoea and episodic oxygen desaturation may induce life-threatening cardiac arrhythmias in non-surgical patients [25]. As the amount of REM sleep and the intensity of its phasic events increase in the postoperative period with simultaneous episodic hypoxaemia and haemodynamic instability, postoperative REM sleep rebound may be particularly dangerous and lead to postoperative myocardial ischaemia, infarction and eventually to unexpected postoperative death. This hypothesis warrants further study, but is supported by the finding that the majority of unexpected postoperative deaths occurred at night [63].

Postoperative impairment of mental function is a common complication in the elderly, with an incidence of 7–77% after major surgery and a peak incidence in the middle of the first week after operation [1, 48, 53, 62]. The pathogenic mechanisms are not completely understood [1, 48, 53, 62], but factors such as hypoxaemia [1, 62] and sleep disturbances [27] may be important. After sleep deprivation in non-surgical volunteers, impaired mental performance has been demonstrated on a simple reaction time test [8, 23], as decreased ability for creative thinking [31], and by impaired ability to perform other cognitive functions [31]. The performance deficit is related to age [30] and to loss of sleep *per se* rather than to changes in the composition of sleep [8, 23]. Mood is affected also by sleep deprivation with decreased vigour and an increase in the subjective feelings of sleepiness [2, 23, 30] and fatigue [30]. As the postoperative sleep disturbances are pronounced and of the same magnitude as in the above-mentioned studies in volunteers, postoperative sleep disturbance may be an important contributing factor in the development of postoperative cerebral dysfunction. Furthermore, postoperative sleep disturbance could be a contributing factor in the phenomenon of postoperative fatigue [11], although a direct relationship between postoperative fatigue and sleep abnormalities remains to be demonstrated.

Prevention and treatment of postoperative sleep disturbances

As the magnitude and duration of the surgical procedure determines the degree of postoperative sleep disturbance [9, 17], a reduction in the surgical stress response by minimally invasive surgery may be effective. So far, there are no comparative studies between sleep patterns after the same operation performed either as a traditional open procedure or by minimally invasive surgical techniques. Stress reduction by neural block with local anaesthetics [35] may be expected to improve postoperative sleep also, but no data are available from studies using continuous nerve block techniques. As previous studies have suggested that pain [13, 49] and morphine [52] disturb postoperative sleep, continuous analgesic techniques with neural block using local anaesthetics without morphine should be evaluated, and the effect of NSAID because of their well-documented opioid-sparing effects. Preliminary studies with ketorolac after lower abdominal surgery have shown decreased opioid requirements and increased quality of sleep on the first postoperative night [56].

Noise [7, 13, 20], nocturnal nursing procedures [29], starvation [45] and increased room temperature [43] are sleep disturbing factors that could be eliminated in the postoperative period.

It has been reported that about 30% of medical and 88% of surgical patients receive sedative drugs during hospitalization [57]. Some of the most commonly used drugs are benzodiazepines, which have an important influence on sleep architecture with attenuated REM sleep and SWS, and increased stage 2 sleep [16]. Recent studies have suggested that the newer hypnotics zopiclone and zolpidem are less likely to alter sleep architecture [16] and that they may increase REM sleep and SWS to a normal level in non-surgical patients with disturbed sleep (insomnia) [16, 50]. The effect of these drugs on the postoperative sleep pattern is unknown and should be evaluated in future clinical trials.

As previously mentioned, patients with sleep apnoea syndrome are more susceptible to respiratory depression after sedative and narcotic administration [12] and the significance of the sleep apnoea syndrome as a surgical risk factor [61] should therefore be explored in future studies.

In summary, postoperative sleep disturbances represent an important research field, as they may have a significant negative impact on postoperative outcome.

References

1. Aakerlund LP, Rosenberg J. Postoperative delirium: treatment with supplementary oxygen. *British Journal of Anaesthesia* 1994; 72: 286–290.
2. Agnew HW, Webb WB, Williams RL. Comparison of stage four and 1-REM sleep deprivation. *Perceptual and Motor Skills* 1967; 24: 851–858.
3. Åkerstedt T, Hume K, Minors D, Waterhouse J. The meaning of good sleep: a longitudinal study of polysomnography and subjective sleep quality. *Journal of Sleep Research* 1994; 3: 152–158.
4. Aurell J, Elmqvist D. Sleep in the surgical intensive care unit: continuous polygraphic recording of sleep in nine patients receiving postoperative care. *British Medical Journal* 1985; 290: 1029–1032.
5. Balogh D, Kittinger E, Benzer A, Hackl JM. Noise in the ICU. *Intensive Care Medicine* 1993; 19: 43–46.
6. Beal AL, Cerra FB. Multiple organ failure syndrome in the 1990s: systemic inflammatory response and organ dysfunction. *Journal of the American Medical Association* 1994; 271: 226–233.
7. Beydon L, Rauss A, Lofaso F, Liu N, Cherqui D, Goldenberg F, Bonnet F. Assessment of the quality of perioperative sleep: study of the factors favouring insomnia. *Annales Françaises D'Anesthésie et de Réanimation* 1994; 13: 669–674.
8. Bonnett MH. Performance and sleepiness following moderate sleep disruption and slow wave sleep deprivation. *Physiology and Behavior* 1986; 37: 915–918.
9. Brimacombe J, Macfie AG. Peri-operative nightmares in surgical patients. *Anaesthesia* 1993; 48: 527–529.
10. Broughton R, Baron R. Sleep patterns in the intensive care unit and on the ward after acute myocardial infarction. *Electroencephalography and Clinical Neurophysiology* 1978; 45: 348–360.
11. Christensen T, Kehlet H. Postoperative fatigue. *World Journal of Surgery* 1993; 17: 215–219.
12. Chung F, Crago RR. Sleep apnoea syndrome and anaesthesia. *Canadian Anaesthetists Society Journal* 1982; 29: 439–445.
13. Close SJ. Patients' night-time pain, analgesic provision and sleep after surgery. *International Journal of Nursing Studies* 1992; 29: 381–392.
14. Cortelli P, Parchi P, Sforza E, Contin M, Pierangeli G, Barletta G, Lugaresi E. Cardiovascular autonomic dysfunction in normotensive awake subjects with obstructive sleep apnoea syndrome. *Clinical Autonomic Research* 1994; 4: 57–62.
15. Douglas NJ, White DP, Pickett CK, Weil JV, Zwillich CW. Respiration during sleep in normal man. *Thorax* 1982; 37: 840–844.
16. Eisen J, MacFarlane J, Shapiro C. Psychotropic drugs and sleep. *British Medical Journal* 1993; 306: 1331–1334.
17. Ellis BW, Dudley HAF. Some aspects of sleep research in surgical stress. *Journal of Psychosomatic Research* 1976; 20: 303–308.
18. Etches RC. Respiratory depression associated with patient-controlled analgesia: a review of eight cases. *Canadian Journal of Anaesthesia* 1994; 41: 125–132.
19. Fehm HL, Benkowitsch R, Kern W, Fehm-Wolfsdorf G, Pauschinger P, Born J. Influences of corticosteroids, dexamethasone and hydrocortisone on sleep in humans. *Neuropsychobiology* 1986; 16: 198–204.
20. Fontaine DK. Measurement of nocturnal sleep patterns in trauma patients. *Heart and Lung* 1989; 18: 402–410.
21. Friess E, von Bardeleben U, Wiedemann K, Lauer CJ, Holsboer F. Effects of pulsatile cortisol infusion on sleep-EEG and nocturnal growth hormone release in healthy men. *Journal of Sleep Research* 1994; 3: 73–79.
22. Gill NP, Wright B, Reilly CS. Relationship between hypoxaemic and cardiac ischaemic events in the perioperative period. *British Journal of Anaesthesia* 1992; 68: 471–473.
23. Gillberg M, Åkerstedt T. Sleep restriction and SWS-suppression: effects on daytime alertness and night-time recovery. *Journal of Sleep Research* 1994; 3: 144–151.
24. Giubilei F, Iannilli M, Vitale A, Pierallini A, Sacchetti ML, Antonini G, Fieschi C. Sleep patterns in acute ischaemic stroke. *Acta Neurologica Scandinavica* 1992; 86: 567–571.
25. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. *American Journal of Cardiology* 1983; 52: 490–494.
26. Hanly PJ, Millar TW, Steljes DG, Baert R, Frais MA, Kryger MH. Respiration and abnormal sleep in patients with congestive heart failure. *Chest* 1989; 96: 480–488.
27. Helton MC, Gordon SH, Nunnery SL. The correlation

between sleep deprivation and the intensive care unit syndrome. *Heart and Lung* 1980; **9**: 464–468.
28. Hilakivi I. Biogenic amines in the regulation of wakefulness and sleep. *Medical Biology* 1987; **65**: 97–104.
29. Hilton BA. Quantity and quality of patients' sleep and sleep-disturbing factors in a respiratory intensive care unit. *Journal of Advanced Nursing* 1976; **1**: 453–468.
30. Horne JA. Sleep function, with particular reference to sleep deprivation. *Annals of Clinical Research* 1985; **17**: 199–208.
31. Horne JA. Sleep loss and "divergent" thinking ability. *Sleep* 1988; **11**: 528–536.
32. Jones JG, Vucevic M. Not awake, not asleep, not dead? *Intensive Care Medicine* 1992; **18**: 67–68.
33. Kapas L, Hong L, Cady AB, Opp MR, Postlethwaite AE, Seyer JM, Krueger JM. Somnogenic, pyrogenic and anorectic activities of tumor necrosis factor-alpha and TNF-alpha fragments. *American Journal of Physiology* 1992; **263**: R708–R715.
34. Kavey NB, Altshuler KZ. Sleep in herniorrhaphy patients. *American Journal of Surgery* 1979; **138**: 682–687.
35. Kehlet H. Modification of responses to surgery by neural blockade: Clinical implications. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*, 2nd Edn. Philadelphia: J. B. Lippincott, 1988; 145–188.
36. Kent S, Price M, Satinoff E. Fever alters characteristics of sleep in rats. *Physiology and Behavior* 1988; **44**: 709–715.
37. Kerkhofs M, Linkowski P, Mendlewicz J. Effects of intravenous catheter on sleep in healthy men and in depressed patients. *Sleep* 1989; **12**: 113–119.
38. Knill RL, Moote CA, Rose EA, Skinner MI. Marked hypoxemia after gastroplasty due to disorders of breathing in REM sleep. *Anesthesiology* 1987; **67**: 3A.
39. Knill RL, Moote CA, Skinner MI, Rose EA. Anesthesia with abdominal surgery leads to intense REM sleep during the first postoperative week. *Anesthesiology* 1990; **73**: 52–61.
40. Knill RL, Skinner MI, Novick TV. Intense REM sleep causes haemodynamic instability. *Canadian Journal of Anaesthesia* 1991; **38**: A17.
41. Knill RL, Skinner MI, Novick T, Vandenberghe HM, Moote CA. The night of intense REM sleep after anaesthesia and surgery increases urinary catecholamines. *Canadian Journal of Anaesthesia* 1990; **37**: S12.
42. Lehmkuhl P, Prass D, Pichlmayr I. General anaesthesia and postnarcotic sleep disorders. *Neuropsychobiology* 1987; **18**: 37–42.
43. Libert JP, Bach V, Johnson LC, Ehrhart J, Wittersheim G, Keller D. Relative and combined effects of heat and noise on sleep in humans. *Sleep* 1991; **14**: 24–31.
44. Lin CC. Effect of nasal CPAP on ventilatory drive in normocapnic and hypercapnic patients with obstructive sleep. *European Respiratory Journal* 1994; **7**: 2005–2010.
45. MacFadyen UM, Oswald I, Lewis SA. Starvation and human slow wave sleep. *Journal of Applied Physiology* 1973; **35**: 391–394.
46. McNamara SG, Grunstein RR, Sullivan CE. Obstructive sleep apnoea. *Thorax* 1993; **48**: 754–764.
47. Mancia G. Autonomic modulation of the cardiovascular system during sleep. *New England Journal of Medicine* 1993; **328**: 347–349.
48. Marcantonio ER, Goldman L, Mangione CM, Ludwig LE, Muraca B, Haslauer CM, Donaldson MC, Whittemore AD, Sugarbaker DJ, Poss R, Haas S, Cook EF, Orav EJ, Lee TH. A clinical prediction rule for delirium after elective noncardiac surgery. *Journal of the American Medical Association* 1994; **271**: 134–139.
49. Moldofsky H, Lue FA, Smythe HA. Alpha EEG sleep and morning symptoms in rheumatoid arthritis. *Journal of Rheumatology* 1983; **10**: 373–379.
50. Monti JM. Effect of zolpidem on sleep in insomniac patients. *European Journal of Clinical Pharmacology* 1989; **36**: 461–466.
51. Moote CA, Knill RL. Isoflurane anesthesia causes a transient alteration in nocturnal sleep. *Anesthesiology* 1988; **69**: 327–331.
52. Moote CA, Knill RL, Skinner MI, Rose EA. Morphine disrupts nocturnal sleep in a dose-dependent fashion. *Anesthesia and Analgesia* 1989; **68**: S200.
53. O'Keeffe ST, Chonchubhair AN. Postoperative delirium in the elderly. *British Journal of Anaesthesia* 1994; **73**: 673–687.
54. Opp MR, Krueger JM. Interleukin 1-receptor antagonist blocks interleukin 1-induced sleep and fever. *American Journal of Physiology* 1991; **260**: R453–R457.
55. Opp M, Obal F, Krueger JM. Corticotropin-releasing factor attenuates interleukin 1-induced sleep and fever in rabbits. *American Journal of Physiology* 1989; **257**: R528–R535.
56. Parker RK, Holtmann B, Smith I, White PF. Use of ketorolac after lower abdominal surgery. *Anesthesiology* 1994; **80**: 6–12.
57. Perry SW, Wu A. Rationale for the use of hypnotic agents in a general hospital. *Annals of Internal Medicine* 1984; **100**: 441–446.
58. Rechtschaffen A, Kales A. *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. Bethesda, MD: US Department of Health, Education and Welfare, 1968.
59. Reeder MK, Muir AD, Foëx P, Goldman MD, Loh L, Smart D. Postoperative myocardial ischaemia: temporal association with nocturnal hypoxaemia. *British Journal of Anaesthesia* 1991; **67**: 626–631.
60. Richards KC, Bairnsfather L. A description of sleep patterns in the critical care unit. *Heart and Lung* 1988; **17**: 35–42.
61. Rosenberg J, Kehlet H. Postoperative episodic oxygen desaturation in the sleep apnoea syndrome. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 368–369.
62. Rosenberg J, Kehlet H. Postoperative mental confusion—association with postoperative hypoxaemia. *Surgery* 1993; **114**: 76–81.
63. Rosenberg J, Pedersen NH, Ramsing T, Kehlet H. Circadian variation in unexpected postoperative death. *British Journal of Surgery* 1992; **79**: 1300–1302.
64. Rosenberg J, Rasmussen V, von Jessen F, Ullstad T, Kehlet H. Late postoperative episodic and constant hypoxaemia and associated ECG-abnormalities. *British Journal of Anaesthesia* 1990; **65**: 684–691.
65. Rosenberg J, Wildschiødtz G, Pedersen MH, von Jessen F, Kehlet H. Late postoperative nocturnal episodic hypoxaemia and associated sleep pattern. *British Journal of Anaesthesia* 1994; **72**: 145–150.
66. Shapiro CM, Flanigan MJ. Function of sleep. *British Medical Journal* 1993; **306**: 383–385.
67. Shibasaki T, Yamauchi N, Hotta M, Imaki T, Oda T, Ling N, Demura H. Brain corticotropin-releasing hormone increases arousal in stress. *Brain Research* 1991; **554**: 352–354.
68. Somers VK, Phil D, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. *New England Journal of Medicine* 1993; **328**: 303–307.
69. Steiger A, Gukdner J, Hemmeter V, Rothe B. Wiedemann K, Holsboer F. Effects of growth hormone-releasing hormone and somatostatin on sleep EEG and nocturnal hormone secretion in male controls. *Neuroendocrinology* 1992; **56**: 566–573.
70. Trachsel L, Schreiber W, Holsboer F, Pollmächer T. Endotoxin enhances EEG alpha and beta power in human sleep. *Sleep* 1994; **17**: 132–139.
71. Wilcox I, Collins FL, Grunstein RR, Hedner J, Kelly DT, Sullivan CE. Relationship between chemosensitivity, obesity and blood pressure in obstructive sleep apnoea. *Blood Pressure* 1994; **3**: 47–54.

British Journal of Anaesthesia 1996; **76**: 560–562

SHORT COMMUNICATIONS

Effect of apparatus on functional residual capacity

G. B. DRUMMOND

Summary

As the route of breathing and use of airway apparatus such as mask, mouthpiece and noseclip can alter breathing pattern, this study has used the helium dilution method to estimate the effects of mouthpiece and mask breathing on functional residual capacity (FRC) in the supine position, and the change in FRC that occurs between the sitting and supine positions while breathing by mouthpiece. In 13 normal subjects, breathing by mouthpiece, FRC was smaller, by a median of 1.07 litre (interquartile values 0.73–1.43 litre) in the supine compared with the sitting position ($P < 0.01$), but residual volume (RV) did not change significantly. FRC measured in the supine position was significantly greater when breathing by mask than by mouthpiece (0.25, 0.04–0.38 litre) and RV was greater by similar amounts (0.20, −0.02 to 0.49 litre). This difference may result from increased inspiratory activity while breathing via the mask. (*Br. J. Anaesth.* 1996; **76**: 560–562)

Key words

Lung, volume. Lung, functional residual capacity. Equipment, masks anaesthesia. Equipment, breathing systems.

Although functional residual capacity (FRC) in adults is commonly thought to be determined passively by the opposing elastic forces of the lung and chest wall, evidence has accumulated that muscle action influences FRC. Reduction of muscle action, by sleep [1], small doses of neuromuscular blockers or induction of anaesthesia may reduce FRC [2]. Consequently, factors that affect the amount and pattern of respiratory muscle activity may affect FRC. Devices such as masks, noseclips and mouthpieces which alter the route of breathing also affect the pattern of breathing [3], and the activity of upper airway muscles is altered by changes in the route of respiration and by posture [4].

The relationship between airway apparatus and FRC has not been studied well, although interventions in patients such as nasal packing or jaw wiring can alter FRC [5]. Previous studies have used a variety of apparatus which may have affected the reported observations and hence the experimental conclusions. This study was designed to investigate the influence of breathing either via a mask or a mouthpiece on FRC in normal subjects. The influence of body position was included to allow comparison with a manoeuvre that is known to affect lung volume.

Methods and results

I recruited 13 healthy, non-smokers, with no respiratory disease, who were not obese. The study was approved by the local Ethics Committee. All patients were familiar with the respiratory apparatus and none had eaten recently. They were not told of the aim of the study, only that their lung volumes would be measured under three conditions.

FRC was measured using helium dilution, with a 10-litre, water-sealed, valveless spirometer (Godart, C. F. Palmer) and a katharometer (Cambridge Instruments). The linearity of the katharometer was checked by serial dilution. This procedure was used also to estimate the volume of the spirometer on each occasion. The spirometer was checked for leaks and brought to a steady temperature by running the system for 4 h before the studies started. The speed of the circulation fan was adjusted carefully so that the pressure at the subject connection was exactly atmospheric. The spirometer was filled with air, and helium and oxygen were added in a 4:1 ratio to obtain approximately 10% helium at the start of the measurements. The katharometer output was displayed on a digital voltmeter to obtain a resolution of at least 0.5% of the initial helium concentration. Subjects breathed air via a three-way tap attached to the spirometer, and were switched to the spirometer as close to FRC as possible. If this was not achieved, the appropriate correction was made by reading the error from the spirometer trace. Oxygen was added to maintain the volume of the spirometer constant. Equilibration was assumed when the concentration of helium had not changed for more than 30 s. Duplicate FRC measurements were made in six subjects in the sitting position to estimate the reproducibility of the measurements. The values differed by a median of 0.13 litre (interquartile values −0.11 to 0.34 litre). Because the precision of measurement of FRC is limited, values are given to the nearest 10 ml. An approximate estimate of oxygen consumption was made from the rate of addition of oxygen over the second half of the measurement period.

Three conditions were applied in random order (random number table): sitting upright with the arms supported at the sides, breathing from a flanged

---

G. B. DRUMMOND, FRCA, University Departement of Anaesthetics, Royal Infirmary, Edinburgh EH3 9YW. Accepted for publication: December 5, 1995.

Address for correspondence: Département d'Anésthesie Réanimation, Hopital Henri Mondor, 51 ave du M de Lattre de Tassigny, 94010 Creteil, France.

Table 1 Results of FRC and spirometry measurements. Sitting measurements were made with a mouthpiece

	FRC (litre BTPS)			ERV (litre BTPS)			Oxygen uptake (ml min^{-1} ATPS)		
Patient No.	Sitting mouthpiece	Lying mask	Lying mouthpiece	Sitting mouthpiece	Lying mask	Lying mouthpiece	Sitting mouthpiece	Lying mask	Lying mouthpiece
1	4.54	2.57	2.61	3.15	1.13	1.13	442	378	385
2	3.39	2.37	2.50	2.02	0.94	1.15	421	357	311
3	1.81	1.45	1.37	1.16	0.58	0.51	319	365	313
4	4.10	2.93	2.68	2.13	1.52	1.16	385	316	333
5	3.77	2.90	2.70	2.40	1.25	1.25	369	322	275
6	3.79	2.73	2.35	3.33	0.91	0.95	348	229	248
7	3.20	2.04	2.05	2.25	1.16	1.13	339	198	262
8	3.04	2.83	2.31	1.46	1.05	1.02	383	324	299
9	2.87	2.33	2.22	2.37	0.94	0.87	361	289	269
10	2.59	2.13	1.86	1.83	0.72	0.72	400	317	299
11	4.57	3.68	3.25	2.33	1.39	1.46	331	321	366
12	3.36	2.72	2.43	2.16	1.01	1.11	193	276	252
13	4.26	2.88	2.49	2.70	1.44	1.72	394	488	376
Median	3.04	2.33	2.22	2.02	0.94	0.95	339	289	269
1st quartile	3.39	2.72	2.43	2.25	1.05	1.13	369	321	299
3rd quartile	4.10	2.88	2.61	2.40	1.25	1.16	394	357	333

mouthpiece and with a noseclip attached; lying supine on a soft trolley with the arms supported at the sides and the head in a neutral position on a pillow, breathing from a mouthpiece with a noseclip attached; and supine in the same position but breathing from a mask (Respironics CPAP mask) with a pneumatic rim which covered the mouth and nose, and held in place with a four-strap harness. A leak-free seal was ensured with water-soluble lubricating jelly (KY, Johnson and Johnson). This was tested at the start and end of each measurement by asking the subject to attempt to breathe when the tap outlet was occluded. On each occasion extreme care was taken to adjust the position of the spirometer connection so that there was no tension on the mouth or head of the subject and the subject was comfortable. Before each measurement, subjects breathed room air for at least 10 min until the respiratory pattern had become stable. Subjects were not allowed to sleep or doze during the measurements. At the end of each measurement period, expiratory reserve volume (ERV) was measured in triplicate. This was read from the spirometer chart to the nearest 30 ml. At least 15 min was allowed between FRC measurements for helium washout from the lungs.

The volume of the mask and mouthpiece were estimated by water displacement. For the mask, this was done by holding the mask over the face of three volunteers while in the supine position, with the nostrils sealed with tape and the mouth shut. The mouthpiece had a volume of 37 ml and the mask volumes were 129, 121 and 155 ml in three different subjects. A mean value of 135 ml was taken. These values were subtracted from the FRC values before statistical analysis.

Data were analysed using a spreadsheet (Microsoft Excel, version 5.0) and a statistics package (Minitab version 8.2), run with MS DOS version 6, on a GA-486US computer. Lung volumes (BTPS) are expressed as medians and interquartile values. The following primary paired *a priori* comparisons of FRC and residual volume (RV) were made using the Wilcoxon test: supine *vs* sitting, breathing via the mouthpiece; and breathing either via the mouthpiece or via the mask in the supine position. We expected patient position to have an effect on FRC and oxygen consumption, but not on RV and the null hypothesis was that there would be no difference between measurements made with the mask and mouthpiece. Oxygen consumption was also compared in the same manner.

As expected, there was a significant difference between FRC in the sitting and supine positions (median 1.07, interquartile values 0.73–1.43 litre) ($P < 0.01$) (table 1). RV did not differ significantly (-0.08, -0.30 to 0.37 litre), but oxygen consumption was greater in the sitting position by 77 (12–97) ml min^{-1} ($P < 0.05$).

FRC with the mask was greater than with the mouthpiece in 10 subjects, and less, by a value smaller than 50 ml, in three. The median difference was 0.25 (0.04–0.38) litre ($P < 0.01$). However, ERV was not affected by the route of measurement (median difference 0, -0.07 to 0.04 litre) so that RV was also significantly greater when breathing with the mask (0.20, -0.02 to 0.45) ($P < 0.05$). There was a positive correlation between the difference of FRC and RV between mask and mouthpiece in each subject ($r = 0.83$) and the relationship was close to 1:1.

Oxygen consumption was not different when measured with the mask or mouthpiece (median difference 20, -18 to 46 ml min^{-1}).

Comment

My results suggest that the use of a mouthpiece, and hence the obligatory use of the mouth for the route of respiration, is associated with a consistently smaller FRC and RV than when a mask is used. Both values were less by approximately 0.2 litre. However, the clear relationship between the differences in both FRC and RV suggests that the changes are related and the possibility that there is a common error has to be examined. A leak of helium during measurements with the mask would cause the second measured concentration to be smaller and hence the calculated FRC would be greater. In view of the care taken to ensure a leak-free contact with the face and repeated tests of the mask seal, this possibility is unlikely, although it cannot be discounted. Mask measurements of FRC in the sitting position were not performed because of the problem of ensuring a good seal in this position.

Repeated measurements of FRC in awake and sleeping subjects using a mask and the helium dilution technique have shown similar reproducibility to that found in this study [1]. A decrease of approximately 0.3 litre with REM sleep was found compared with the awake state.

The use of different types of airway apparatus such as noseclips, mouthpieces and masks alters the pattern of breathing, in comparison with measurements made using non-invasive methods, such as inductance bands.

Both body posture and route of breathing affect the activity of the muscles of the upper airway [4]. It is not clear if the route of breathing, or the apparatus used to measure breathing, also affects respiratory muscles that influence FRC. Although it is widely appreciated that body posture affects FRC, the predominant explanation offered for this effect is a mechanical one, attributing the greater FRC in the upright posture to the inspiratory effect of the abdominal contents. However, in the upright position abdominal muscles are active and thus FRC is not determined only by passive elastic forces. FRC is reduced by interventions that reduce muscle activity such as partial neuromuscular block [2]. Breathing through the nose, which is the usual route when both are available, is associated with activation of upper airway muscles [6]. In patients, nasal packing causes a decrease in FRC, and jaw wiring causes an increase in FRC [5]. To fully elucidate the possibility that there is activation of inspiratory muscles during mask breathing it would have been of interest to measure inspiratory reserve volume and ERV. However, when the study was designed it was the subdivisions of FRC that were considered of interest and the study did not include a vital capacity manoeuvre during the FRC measurements.

Measurements of oxygen consumption were not directly relevant, but showed that the sitting position was associated with significantly greater oxygen consumption, which is presumably caused by greater postural muscle activity. Previous studies of FRC have not always reported the type of apparatus used. The effect noted in this study is comparable with the changes in FRC found by some investigators and clearly could affect the magnitude of the observations of previous studies, and perhaps explain some of the discrepancies found in earlier investigations.

References

1. Hudgel DW, Devadatta P. Decrease in functional residual capacity during sleep in normal humans. *Journal of Applied Physiology* 1984; 57: 1319–1322.
2. De Troyer A, Martin JG. Respiratory muscle tone and the control of functional residual capacity. *Chest* 1983; 84: 3–4.
3. Perez W, Tobin MJ. Separation of factors responsible for change in breathing pattern induced by instrumentation. *Journal of Applied Physiology* 1985; 59: 1515–1520.
4. Douglas NJ, Jan MA, Yildirim N, Warren PM, Drummond GB. Effect of posture and breathing route on genioglossal EMG activity in normal subjects and in patients with the sleep apnoea/hypopnea syndrome. *American Review of Respiratory Disease* 1993; 148: 1341–1345.
5. Swift AC, Campbell IT, McKown TM. Oronasal obstruction, lung volumes, and arterial oxygenation. *Lancet* 1988; i: 73–75.
6. Basner RC, Simon PM, Schwartzstein RM, Weinberger SE, Weiss JW. Breathing route influences upper airway muscle activity in awake normal adults. *Journal of Applied Physiology* 1989; 66: 1766–1771.

British Journal of Anaesthesia 1996; **76**: 563–564

Measurement technique and variation in intramucosal pH

P. R. WOOD AND P. G. P. LAWLER

Summary

We have calculated gastric intramucosal pH (pH_i) from Trip catheter saline tonometered samples in two patients undergoing ventilation using four different sampling techniques, each repeated five times. pH_i was calculated from measurement of $P\text{CO}_2$ in tonometered saline ($T\text{CO}_2$). $T\text{CO}_2$ was measured immediately, and then at 6-min intervals for 30 min. Variation in measurement was greatest for capped syringes stored at room temperature, and least when stored uncapped on ice. $T\text{CO}_2$ always decreased significantly within 12 min. The mean difference in pH_i (all sampling techniques) over 30 min was 0.1005 pH units. The results indicate that the calculated pH_i was subject to variation as a result of both the method of sample storage and delay in measurement. An error of ±0.1 pH units may have clinically important implications if pH_i is used to monitor either severity of illness or efficiency of resuscitation. (*Br. J. Anaesth.* 1996; **76**: 563–564)

Key words

Gastrointestinal tract, pH. Monitoring, pH oesophageal.

The use of a Trip tonometer (Tonometrics, Inc., Bethesda, MD, USA) to measure gastric intramucosal pH (pH_i) is a recent innovation in intensive care medicine. A Trip nasogastric catheter incorporates a saline-filled balloon, which lies in contact with the gastric mucosa. Diffusion of carbon dioxide from gastric mucosa, into saline, allows for its subsequent measurement ($T\text{CO}_2$) using a conventional blood-gas analyser. An arterial blood-gas sample is obtained concurrently, and the measured bicarbonate (HCO_3) used to determine pH_i indirectly using a slide rule nomogram, supplied with the tonometer. pH_i is said to be an indicator of organ-specific oxygen and substrate delivery and may reveal splanchnic hypoperfusion, a situation of potential critical importance in clinical shock [1, 2].

Priming with saline, and subsequent sampling of the Trip catheter (deadspace = 1.5 ml, sample volume = 2.5 ml), may produce error if air is introduced into the system. Any delay between sampling and measurement may also affect the derived result, a situation well recognized with arterial blood-gas analysis [3]. We tested this possibility by calculating pH_i using different sample conditions and measurement times.

Methods and results

Local Ethics Committee approval was obtained before the study. Measurements were made in two stable patients undergoing ventilation who received i.v. H_2 receptor antagonists (ranitidine) throughout the period of investigation. Nasogastric feeding was suspended for 2 h before sampling. The Trip saline prime was allowed to equilibrate *in vivo* for 90 min before analysis.

Arterial blood-gas and tonometered saline samples were obtained and processed by one investigator using an IL 1312 blood-gas analyser, located within the intensive care unit (ITU). The Trip catheter was re-primed immediately after sample withdrawal.

$T\text{CO}_2$ was measured within 30 s of sampling (0 min), and arterial blood-gas 3 min later, between which the analyser self-calibrated automatically. The measurements were then repeated on the same sample pair, every 6 min for a total of 30 min, during which each individual sample was stored under one of four conditions (all collected in a 2-ml disposable plastic syringe): (1) capped, room temperature; (2) capped, on ice; (3) uncapped, room temperature; and (4) uncapped, on ice.

Accuracy of timing between sampling was ensured by the use of a stop clock and verified by the results print-out from the automatic blood-gas analyser. Each condition was studied exclusively five times during a single 24-h period, producing a total study period of 4 days. Before each series of measurements the blood-gas analyser was subject to a two-point calibration. Under these conditions the reproducibility of recurrent $P\text{CO}_2$ measurement (equivalent to electrode re-calibration drift) was less than 0.01 kPa.

All measurements within each condition were averaged and mean values at time = 0 min and time = 30 min were compared using a paired t test. $P < 0.05$ was considered significant.

The influence of time on $T\text{CO}_2$, pH_i and arterial HCO_3 is shown for each condition in table 1. The mean value of $T\text{CO}_2$ at $t = 0$ varied by as much as 1 kPa depending on the sampling condition, but the subsequent downward trend over 30 min was seen with each technique, reaching significance at 12 min

---

P. R. WOOD, MB, BCH, FRCA, Major Injuries Unit, Selly Oak Hospital, Raddlebarn Road, Selly Oak, Birmingham B29 6TD. P. G. P. LAWLER, FRCP, FRCA, South Cleveland Hospital, Middlesbrough TS4 3BW. Accepted for publication: December 12, 1995.

Correspondence to P.R.W.

Table 1 Variation in bicarbonate, tonometered carbon dioxide and pH_i at $t = 0$ and $t = 30$ with sample technique (mean (SD))

Sample technique	HCO_3 (mmol litre^{-1})			T_{CO_2} (kPa)			pH_i		
	$t = 0$	$t = 30$	P	$t = 0$	$t = 30$	P	$t = 0$	$t = 30$	P
Capped, room temperature	27.820 (1.201)	27.360 (1.861)	0.315	5.678 (0.765)	4.172 (0.393) (26.521 %)	0.001	7.396 (0.043)	7.518 (0.013) (1.649 %)	0.000
Capped, ice	26.660 (1.137)	26.200 (1.153)	0.004	6.334 (1.312)	4.992 (1.288) (21.190 %)	0.003	7.328 (0.107)	7.434 (0.129) (1.447 %)	0.007
Uncapped, room temperature	24.300 (0.644)	23.940 (0.594)	0.266	5.318 (0.609)	4.288 (0.442) (19.364 %)	0.012	7.364 (0.062)	7.452 (0.035) (1.195 %)	0.022
Uncapped, ice	24.940 (0.270)	24.760 (0.358)	0.195	5.168 (0.217)	4.336 (0.291) (16.099 %)	0.005	7.372 (0.038)	7.458 (0.028) (1.166 %)	0.005

($P < 0.05$). pH_i increased under all conditions, with highly significant and clinically important increases at 30 min ($P < 0.02$).

The initial calculated pH_i of 7.365 (mean of all values) increased by a mean of 0.1005 pH units at 30 min (minimum increase 0.086, uncapped ice; maximum 0.122, capped, room temperature), as a result of changes in measured T_{CO_2}. The increases were significant at 12 min in all but one condition (uncapped ice), which became significant at 18 min. There was no statistically significant change in measured arterial bicarbonate over 30 min, with the exception of capped ice samples ($P = 0.004$).

Comment

We have demonstrated that T_{CO_2} measurement and subsequent pH_i calculation is subject to variation, depending on the sampling technique. The variation in mean T_{CO_2} at $t = 0$ is explained, we believe, by our methodology which studied each individual sampling technique on a different day, and was therefore subject to patient variation. However, a subsequent drift in measured T_{CO_2} occurred with all four conditions. This corresponded to a change in calculated hydrogen ion concentration over 30 min of 24.6 %, 21.7 %, 18.5 % and 18.1 % for conditions 1 to 4, respectively (mean of all four sample types = 20.72 %), the change in acidity being disguised by the unit of measurement (pH).

In practice, measurements of arterial blood gases are often delayed. Our results demonstrated that delays in measurement, particularly of T_{CO_2}, and hence calculated pH_i, may have significant implications for the diagnosis and monitoring of resuscitation.

A pH change of 0.1005 units (mean increase in all samples over 30 min) would at a pH value of approximately 7.35, produce alternative values of 7.25 or 7.45. As a pH_i value of less than 7.35 is considered pathological [4] errors of this nature and magnitude are worrying. Our patients were stable and never clinically shocked and therefore we do not know if the measurement changes that we have documented become more or less significant when pH_i is pathologically low.

In this study a significant problem with drift in arterial bicarbonate measurement occurred only with the capped ice samples, but as pH_i is calculated from the HCO_3/T_{CO_2} ratio, any drift in this variable is yet another potential source of concern. The accuracy of measurement of T_{CO_2} can be improved by using a phosphate buffered solution [5] but prompt analysis would still be advised. An additional acknowledged difficulty is the error attributable to the choice of blood-gas analyser [6].

We suggest that strict standardization of the conditions of measurement for both arterial blood gases and the tonometered sample is necessary before results gained from Trip analysis may be usefully applied in, and between, different intensive care patient groups.

References

1. Fiddian-Green RG. Role of the gut in shock and resuscitation. *Baillière's Clinical Anaesthesiology* 1991; 5: 75–99.
2. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Critical Care Medicine* 1992; 20: 864–874.
3. Kelman GR, Nunn JF. Nomograms for correction of blood P_{O_2}, P_{CO_2}, pH, and base excess for time and temperature. *Journal of Applied Physiology* 1966; 21: 1484–1490.
4. Doglio GR, Pusajo JF, Egurrola MA, Bonfigli GC, Parra C, Vetare L, Hernandes MS, Fernandez S, Palizar F, Gutierrez G. Gastric mucosal pH as a prognostic index of mortality in critically ill patients. *Critical Care Medicine* 1991; 19: 1037–1040.
5. Knichwitz G, Mertes N, Kuhmann M. Improved PCO_2 measurement in six standard blood gas analysers using a phosphate-buffered solution for gastric tonometry. *Anaesthsia* 1995; 50: 532–534.
6. Riddington D, Venkatesh B, Clutton-Brock T, Bion J. Potential hazards in estimation of gastric intramucosal pH. *Lancet* 1992; 340: 547.

British Journal of Anaesthesia 1996; **76**: 565–566

Magnesium sulphate enhances residual neuromuscular block induced by vecuronium

T. FUCHS-BUDER AND E. TASSONYI

Summary

Magnesium sulphate ($MgSO_4$) is currently used for haemodynamic control during anaesthesia and the early postoperative period. We have investigated the effect of this treatment on residual neuromuscular block after administration of vecuronium. Twenty adult patients were allocated randomly to one of two groups to receive $MgSO_4$ 60 mg kg^{-1} either at recovery from vecuronium block to a train-of-four (TOF) ratio of 0.7, or 1 h after recovery to a TOF ratio of 0.7. Neuromuscular transmission was monitored using electromyography and TOF stimulation. $MgSO_4$ caused rapid and profound recurarization in all 20 patients. $MgSO_4$ decreased the amount of acetylcholine released at the motor nerve terminal and thus may lead to recurarization in patients previously exposed to neuromuscular blocking agents. (*Br. J. Anaesth.* 1996; **76**: 565–566)

Key words

Neuromuscular block, vecuronium. Neuromuscular block, recovery. Ions, magnesium. Measurement techniques, electromyography.

Magnesium sulphate ($MgSO_4$) may be given during anaesthesia and the early postoperative period for its antihypertensive and anti-arrhythmic properties [1, 2]. While the effect of $MgSO_4$ pretreatment on the pharmacodynamics of neuromuscular blocking agents has been reported [3], less is known about its effects when given after neuromuscular block has recovered clinically (i.e. TOF ratio $\geqslant 0.7$). This question may be of clinical relevance as $MgSO_4$ decreases the amount of acetylcholine (ACh) released at the motor nerve terminal, thus reducing the safety margin of neuromuscular transmission. We therefore hypothesized that $MgSO_4$ may enhance residual neuromuscular block. The aim of the present study was to determine if $MgSO_4$ administration at different times after recovery to a TOF ratio of 0.7 is safe.

Methods and results

After obtaining institutional Ethics Committee approval and written informed consent, we studied 20 patients, ASA I or II, undergoing elective surgery. We excluded patients with known neuromuscular disease or receiving medications influencing neuromuscular function. After premedication with midazolam 7.5 mg, patients were anaesthetized with fentanyl 2–3 μg kg^{-1}, thiopentone 4–5 mg kg^{-1} and 1% isoflurane with 60% nitrous oxide in oxygen. Patients' lungs were ventilated to normocapnia and skin temperature over the adductor pollicis was maintained greater than 34 °C. Neuromuscular function was assessed by supramaximal stimulation of the ulnar nerve with TOF stimuli at 2 Hz every 20 s and recording the electromyographic response (twitch height, TOF ratio) of the adductor pollicis muscle (Relaxograph, Datex Instrumentarium Corporation, Finland). When the end-tidal isoflurane concentration had stabilized, the Relaxograph was recalibrated, the control twitch height (first response of TOF) determined, and vecuronium 100 μg kg^{-1} administered. Patients were allocated randomly to one of two groups of 10 each to receive $MgSO_4$ 60 mg kg^{-1} in saline 100 ml as a short infusion either at recovery to a TOF ratio of 0.7 or 1 h after recovery to a TOF ratio of 0.7. The onset of recurarization (time from end of perfusion of $MgSO_4$ to minimum twitch height), minimum twitch height, number of TOF responses at minimum twitch height, and time to recovery of the TOF ratio to 0.7 again, were recorded.

The typical time course of vecuronium neuromuscular block and subsequent effect of $MgSO_4$ are shown in figure 1. In the group that received $MgSO_4$ at a TOF ratio of 0.7, the following values were recorded before administration of $MgSO_4$: mean twitch height 78 (SD 3)% and TOF ratio 0.71 (0.02). Onset of maximal block was 328 (79) s, minimum twitch height was 23.5 (11)%, median number of TOF responses at minimum twitch height was 2 (range 0–4) and time to recovery to a TOF ratio of 0.7 was 28.8 (10.5) min. In patients who received $MgSO_4$ 1 h after recovery to a TOF ratio of 0.7 the following values were obtained: twitch height 88 (6)%, TOF ratio 0.87 (0.14), onset of maximal block 480 (120) s, minimum twitch height 34 (20)%, median number of TOF responses at minimum twitch height 3 (range 2–4) and time to recovery to TOF 0.7 22 (7.6) min.

T. FUCHS-BUDER*, MD, E. TASSONYI, MD, Department of Anaesthesiology, Geneva University Hospital, Switzerland. Accepted for publication: November 2, 1995.

*Address for correspondence: Department of Anaesthesiology, Geneva University Hospital, CH-1211 Geneva 14, rue Micheli-du-Crest 24, Switzerland.

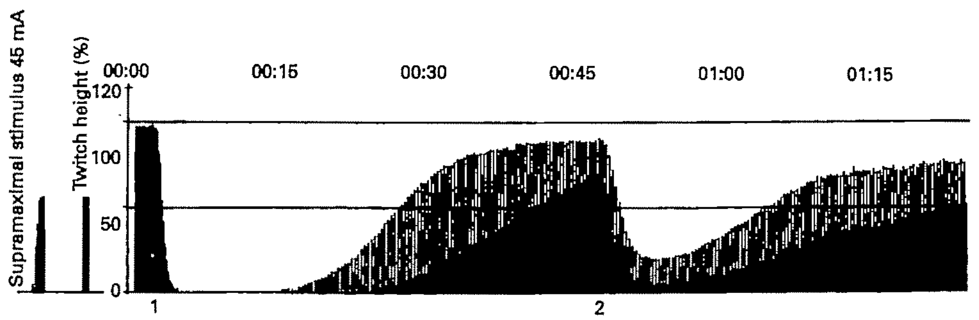


Figure 1 Time course of vecuronium neuromuscular block and $MgSO_4$-induced recurarization: 1 = administration of vecuronium 100 μg kg^{-1}; 2 = recovery of TOF ratio to 0.7 and infusion of $MgSO_4$ 60 mg kg^{-1}.

Comment

This study has demonstrated that administration of $MgSO_4$ after return of neuromuscular function to a TOF ratio of 0.7 leads to recurarization. The risk of muscle paralysis persists, at least during the first hour after recovery to a TOF ratio of 0.7. Recurarization is rapid in onset and profound enough to compromise respiration.

We chose $MgSO_4$ 60 mg kg^{-1} as this dose is used currently in anaesthetic practice [2]. However, at these concentrations, $MgSO_4$ without neuromuscular blockers does not induce measurable block [4].

Decreased ACh release at the motor nerve terminal by $MgSO_4$ is the most likely explanation for the observed recurarization. According to the concept of the margin of safety of neuromuscular transmission [5], the twitch response may be normal with 70–80 % of the ACh receptors at the neuromuscular junction still blocked by a non-depolarizing neuromuscular blocking agent. However, in this situation, any decrease in ACh release may enhance neuromuscular block with subsequent clinical consequences such as recurarization. Patients in the early postoperative period, with a large percentage of ACh receptors still occupied, are particularly vulnerable to drug interaction at the neuromuscular junction.

In summary, $MgSO_4$ in clinically relevant doses caused profound recurarization when given to patients recovered from neuromuscular block. We conclude that when $MgSO_4$ is given in the postoperative period, respiration and neuromuscular function have to be monitored carefully to avoid complications caused by muscle weakness.

References

1. Zaloga G, Eisenach JC. Magnesium, anesthesia, and hemodynamic control. *Anesthesiology* 1991; 74: 1–2.
2. James MFM. Clinical use of magnesium infusions in anesthesia. *Anesthesia and Analgesia* 1992; 74: 129–136.
3. Fuchs-Buder T, Wilder-Smith OHG, Borgeat A, Tassonyi E. Interaction of magnesium sulphate with vecuronium-induced neuromuscular block. *British Journal of Anaesthesia* 1995; 74: 405–409.
4. James MFM, Schenk PA, Van der Veen BW. Priming of pancuronium with magnesium. *British Journal of Anaesthesia* 1991; 66: 247–249.
5. Waud BE, Waud DR. The relation between the response to "train-of-four" stimulation and receptor occlusion during competitive neuromuscular block. *Anesthesiology* 1972; 37: 413–416.

British Journal of Anaesthesia 1996; 76: 567–569

Comparison of the effect of two dose schedules of oral omeprazole with oral ranitidine on gastric aspirate pH and volume in patients undergoing elective surgery

I. D. LEVACK, R. A. BOWIE, D. P. BRAID, A. J. ASBURY, R. L. MARSHALL, K. B. SLAWSON, H. BIRRELL AND K. R. W. GILLON

Summary

We have compared gastric aspirate pH and volume at induction of anaesthesia in 222 patients who had received either omeprazole or ranitidine before elective operations. Omeprazole was given orally either as 40 mg on the evening before and 40 mg on the morning of surgery or as 80 mg on the morning of surgery. Ranitidine 150 mg was given orally on the evening before surgery and 2 h before anaesthesia. Treatment success was defined as aspirate pH $\geqslant 2.5$ and volume < 25 ml at induction of anaesthesia. Treatment was successful in 84% (95% confidence interval (CI) 73–91%) of patients in the omeprazole 40+40 mg group, 84% (95% CI 73–91%) in the ranitidine group and 73% (95% CI 61–83%) in the omeprazole 80 mg group. There were no statistically significant differences between the groups. Twelve patients in the omeprazole 80 mg group had gastric pH < 2.5 and four had volume > 25 ml. Only three patients had a gastric pH < 2.5 in the omeprazole 40+40 mg group and none had volume > 25 ml, which compared well with the ranitidine group. Omeprazole, given as 40 mg in the evening and 40 mg on the morning of operation, has a potential role for use in patients at risk for aspiration during general anaesthesia. (*Br. J. Anaesth.* 1996; **76**: 567–569)

Key words

Antacids, omeprazole. Antacids, ranitidine. Gastrointestinal tract, antacids. Gastrointestinal tract, pH. Gastrointestinal tract, volume.

Acid aspiration, particularly during general or obstetric emergency surgery, is associated with morbidity and mortality [1]. It is generally agreed that patients with gastric contents of pH < 2.5 and volume $\geqslant 25$ ml are at risk of pulmonary damage should aspiration occur. Various pharmacological agents such as H_2 receptor antagonists, antacids and anticholinergics have been used to reduce the risk of aspiration or the risk of pulmonary damage should aspiration occur [2]. Omeprazole is a potent inhibitor of gastric acid secretion, binding irreversibly to the parietal cell proton pump (H^+K^+-ATPase) which is the end-point in the pathway to gastric acid secretion, thus producing long lasting acid inhibition. The use of omeprazole in both its i.v. and oral formulations has been investigated extensively [3].

In this large, multicentre study in patients undergoing elective operations, we have compared the effects of omeprazole in single and divided dose regimens with the H_2 receptor antagonist, ranitidine, on pH and volume of gastric contents.

Methods and results

The study was approved by the Ethics Committees of the five participating hospitals and informed written consent was obtained from all patients.

We studied patients of both sexes, aged 18–70 yr, undergoing elective surgery, in a double-blind, double-dummy, parallel group study. Patients with active oesophageal or peptic ulcer disease, pyloric stenosis and those receiving antisecretory drugs were excluded from the study. Patients were allocated randomly to one of three treatment regimens according to a computer-generated randomized list: omeprazole 80 mg at 06:00 (or 10:00 if surgery was scheduled for after 13:00) on the morning of surgery; omeprazole 40 mg at 20:00 on the evening before surgery and 40 mg at 06:00 (or 10:00 if surgery was scheduled for after 13:00) on the morning of surgery; ranitidine 150 mg at 10:00 on the evening before surgery and ranitidine 150 mg 2 h before anaesthesia. In addition, patients were premedicated in accordance with hospital practice (temazepam, diazepam, lorazepam or morphine). Anaesthesia and tracheal

---

I. D. LEVACK,*, MD, Department of Anaesthesia, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB9 1GS. R. A. BOWIE, MB, CHB, FRCA, Department of Anaesthesia, Victoria Hospital, Hayfield Road, Kirkcaldy, Fife KY2 5AH. D. P. BRAID, MB, CHB, FRCA, A. J. ASBURY, PHD, FRCA, Department of Anaesthesia, Western Infirmary, Glasgow G11 6NT. R. L. MARSHALL, MB, CHB, FRCA, Department of Anaesthesia, Victoria Infirmary, Langside, Glasgow G42 9TY. K. B. SLAWSON†, MB, CHB, FRCA, Department of Anaesthesia, Western General Hospital, Crewe Road, Edinburgh EH4 2XU. H. BIRRELL, BSC, K. R. W. GILLON, BSC, PHD, Astra Clinical Research Unit, 10 Logie Mill, Logie Green Road, Edinburgh EH7 4HG. Accepted for publication: November 21, 1995.

*Present address for correspondence: Department of Anaesthesia, Western General Hospital, Crewe Road, Edinburgh EH4 2XU.

†Present address: Department of Anaesthesia, Eastern General Hospital, Seafield Street, Edinburgh EH6 7LN.

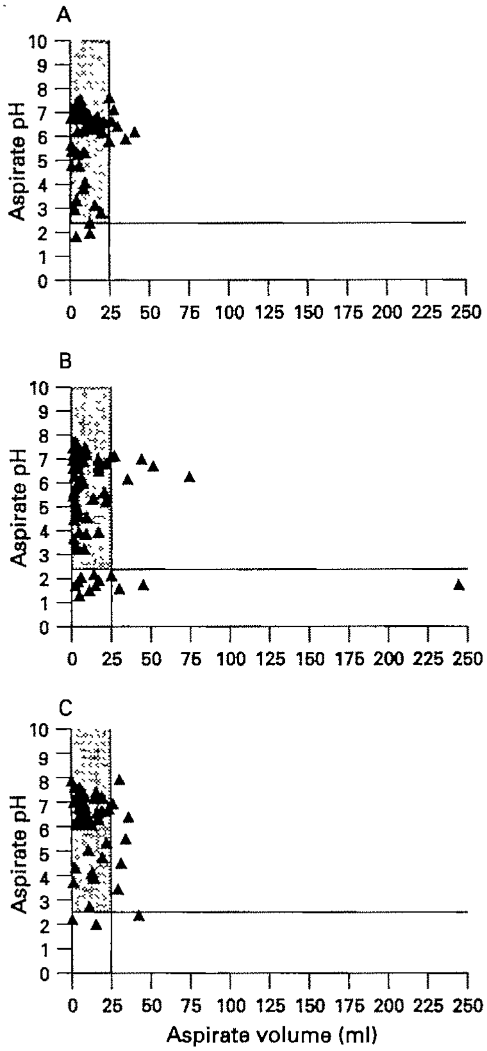


Figure 1 Aspirate pH and volume at induction of anaesthesia. A: Omeprazole 40+40 mg (26 patients with zero volume were not included); B: omeprazole 80 mg (14 patients with zero volume were not included); C: ranitidine 150+150 mg (19 patients with zero volume were not included).

intubation were performed according to normal practice.

Immediately after induction of anaesthesia and insertion of the tracheal tube, a nasogastric tube was inserted into the stomach and its position confirmed by auscultation during insufflation of a small quantity of air down the tube. Gastric contents were aspirated, the time noted and the volume collected was measured. pH was measured in an aliquot of gastric fluid.

The nasogastric tube was removed before recovery from anaesthesia. It was hoped that, by using this method, residual gastric volume would be measured accurately in the majority of patients, although there is a possibility of error in obtaining all of the gastric juice in cases where the volume is small.

Patients were asked if they had been aware of any unusual symptoms in the postoperative period.

Treatment was considered to be successful if the following criteria were achieved: gastric contents of pH $\geqslant 2.5$ and volume < 25 ml at induction of anaesthesia. Results are presented as percentage of patients with a successful treatment, with 95% confidence intervals (CI) in each group.

We recruited 222 patients (74 male). The three treatment groups were well matched for age (mean 43.9 (range 18–70) yr) and weight (67.3 (45.5–110) kg). Randomization was successful, with 74 patients in each omeprazole group and 73 in the ranitidine group. The proportion of females to males was similar in all groups. All patients who received treatment were included in the analysis, except for one case, where surgery was cancelled.

The percentages of patients achieving the success criteria in the treatment groups were 73% (95% CI 61–83%) in the omeprazole 80 mg group, 84% (73–91%) in the omeprazole 40+40 mg group and 84% (73–91%) in the ranitidine group. As the 95% CI for all three groups overlapped, there was no significant difference in success proportions between the treatment groups.

Intragastric pH values relative to intragastric volumes are shown in figure 1. Patients with zero gastric volume were counted as treatment successes in the analysis. Treatment was successful in those patients depicted in the top left quadrants of the graphs, that is with pH $\geqslant 2.5$ and volume < 25 ml. Treatment was successful in the majority of patients in each treatment group. No patient in the omeprazole 40 mg+40 mg group (fig. 1A), four patients in the omeprazole 80 mg group (fig. 1B) and one patient in the ranitidine group (fig. 1C) were considered to be at increased risk from aspiration because of a combination of pH < 2.5 and volume $\geqslant 25$ ml (lower right quadrants of fig. 1).

There were no serious adverse events. Minor adverse events observed or reported by the patients all resolved.

Comment

The majority of patients in each of the treatment groups studied were treated successfully. The percentage success rate was greater in the divided dose omeprazole group and in the ranitidine group compared with the single dose omeprazole group at induction of anaesthesia, but this difference was not statistically significant. These results are similar to those reported from other groups [4, 5]. Although the anaesthetic technique was standardized, there was some variability in anaesthetic agents used between centres and, in particular, premedication, including the use of morphine, which is known to inhibit gastric emptying. However, only three patients received morphine before anaesthesia and all three were treated successfully. It is also possible that patients in the ranitidine group who had operations in the afternoon could have had a failed treatment because of the long interval between the evening and pre-anaesthesia dose. This was not the case as more patients on the morning surgical list had a failed treatment in this group.

This is the first large multicentre study comparing directly omeprazole with ranitidine when given as premedication. Ewart and colleagues reported a single centre study where 70 patients received the same dose regimens of omeprazole and ranitidine as in this study except that the evening dose of omeprazole was given 2 h later at 22:00 [4]. This group also reported high success rates of 100% in the omeprazole group and 94% in the ranitidine group when similar success criteria were applied.

Twelve patients who received a single dose of omeprazole 80 mg had a gastric pH < 2.5 and four also had volume > 25 ml. This suggests that this dose regimen is not sufficiently effective to be recommended for use. Only three patients had pH < 2.5 in the omeprazole divided dose group and none had a volume > 25 ml. These results compare well with the ranitidine group.

There are concerns about what value can be regarded as a safe pH. Crawford [6] has advocated a minimum pH value of at least 3.0, as pH 3.5 has been shown to cause serious pneumonitis. However, calculation of the data from this study using a higher pH value of 3.5 does not substantially affect the results (omeprazole 40 + 40 mg = 80%, omeprazole 80 mg = 71%, ranitidine 150 + 150 mg = 84%).

In conclusion, we have shown that omeprazole 40 mg in the evening and 40 mg on the morning of operation has a potential role for use in patients considered to be at risk of aspiration during general anaesthesia and is well tolerated in this group of patients.

Acknowledgement

This study was supported by a grant from the Astra Clinical Research Unit, Edinburgh, UK.

References

1. Olsson GL, Hallen B, Hambraeus-Jonzon K. Aspiraton during anaesthesia: a computer-aided study of 185358 anaesthetics. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 84–92.
2. Power KJ. The prevention of the acid aspiration (Mendelson's) syndrome. A contribution to reduced maternal mortality. *Midwifery* 1987; 3: 143–148.
3. Rowbotham DJ. Omeprazole—a useful new agent. *British Journal of Anaesthesia* 1990; **65**: 607–608.
4. Ewart MC, Yau G, Gin T, Kotur CF, Oh TE. A comparison of the effects of omeprazole and ranitidine on gastric secretion in women undergoing elective Caesarean section. *Anaesthesia* 1990; **45**: 527–530.
5. Orr DA, Bill KM, Gillon KRW, Wilson CM, Fogarty DJ, Moore J. Effects of omeprazole, with and without metoclopramide, in elective obstetric anaesthesia. *Anaesthesia* 1993; **48**: 114–119.
6. Crawford JS. General analgesia and anaesthesia in obstetrics. In: Ostheimer GW, ed. *Clinics in Anesthesiology, Obstetric Analgesia and Anaesthesia*. London: WB Saunders, 1986, vol. 4(1).

British Journal of Anaesthesia 1996; **76**: 570–572

CASE REPORTS

Unilateral convulsion after induction of anaesthesia with propofol

D. COCHRAN, W. PRICE AND C. L. GWINNUTT

Summary

We report a case in which a 42-yr-old man suffered a unilateral convulsion immediately after i.v. injection of propofol, and was discovered subsequently to have an old contralateral cerebral infarct. This complication and the current information on the relationship between propofol and abnormal neurological activity are discussed. (*Br. J. Anaesth.* 1996; **76**: 570–572)

Key words

Anaesthetics i.v., propofol. Complications, spontaneous excitatory movement.

Since its introduction, propofol has been linked with both pro- and anticonvulsant activity. We describe a case in which a convulsion, limited to the left side of the body, occurred immediately after administration of propofol in a patient who was subsequently shown to have an undiagnosed cerebral infarct. We could not find a previous report of this type of abnormal neurological activity after propofol.

Case report

A 42-yr-old man presented for surgical correction of a Dupuytren's contracture of his right hand during general anaesthesia. The preoperative anaesthetic assessment was unremarkable and he declined any premedication. On arrival in the anaesthetic room, monitoring by pulse oximetry and ECG was commenced, and an i.v. cannula was inserted, after which his lungs were preoxygenated via a Bain coaxial system for approximately 2 min. Anaesthesia was induced with propofol 200 mg. As the injection finished the patient developed irregular jerking movements on his left arm and leg which gradually became more violent and similar to the clonic phase of a grand mal convulsion. This lasted approximately 1 min and resolved spontaneously. Ventilation was unaffected, oxygen was administered continuously and peripheral oxygen saturation remained greater than 95 % throughout. As the episode was brief and resolved spontaneously, it was decided to continue, and anaesthesia was maintained with isoflurane and 65 % nitrous oxide in oxygen. An axillary block of the left arm was performed using 0.25 % bupivacaine 40 ml without adrenaline for postoperative pain relief. During operation he received fentanyl 100 µg when a skin graft was taken from his thigh. There were no further episodes of seizure activity during anaesthesia or recovery.

Because of the unilateral nature of the seizure, a CT scan was performed after operation. This revealed a wedge-shaped, low-density area in the right posterior parietal lobe, consistent with an infarct in the vascular watershed between the territories of the middle and posterior cerebral arteries (fig. 1). On direct questioning, the patient revealed that he had suffered from meningitis at 16 yr of age which had left him with a mild bilateral hearing loss and a slight weakness in his left leg, which had recently resulted in him having to give up playing football. A more detailed neurological examination after these results showed some slight muscle wasting in the left lower leg and an up-going plantar on the left. He suffered no further seizures in hospital and was discharged home.

Discussion

Since 1987 there have been a variety of reports linking propofol with the occurrence of abnormal neurological sequelae, ranging from minor involuntary movements to opisthotonos and grand mal convulsions, both in previously healthy patients and those known to suffer from epilepsy. Excitatory events have been reported on induction of anaesthesia with propofol [1], but appear to be more common during recovery [2–7], in two patients after intervals of 21 h and 5 days between administration of propofol and the convulsions [7, 8]. Although most cases describe single convulsions, status epilepticus and repeated attacks of opisthotonos for 23 days have been reported after anaesthesia, of which propofol was a component [4, 9].

A criticism of these reports is that on many occasions combinations of drugs were administered, making the implication of propofol impossible, as many of the commonly used anaesthetic agents have been reported as being capable of causing clinically evident seizure activity [10]. Propofol has been administered uneventfully to a patient on two occasions but associated with a grand mal convulsion when given with alfentanil on a third occasion [11]. However, in the case reported by Shearer of grand mal convulsions lasting for 3 h, propofol was clearly implicated as it was the only agent administered [12].

The abnormal movements reported after propofol have been labelled as seizures, grand mal convulsions

---

D. COCHRAN, MB, CHB, W. PRICE, MB, BS, C. L. GWINNUTT, MB, BS, FRCA, Department of Anaesthesia, Salford Royal Hospitals NHS Trust, Hope Hospital, Stott Lane, Salford M6 8HD.
Accepted for publication: December 12, 1995.
Correspondence to C. L. G.

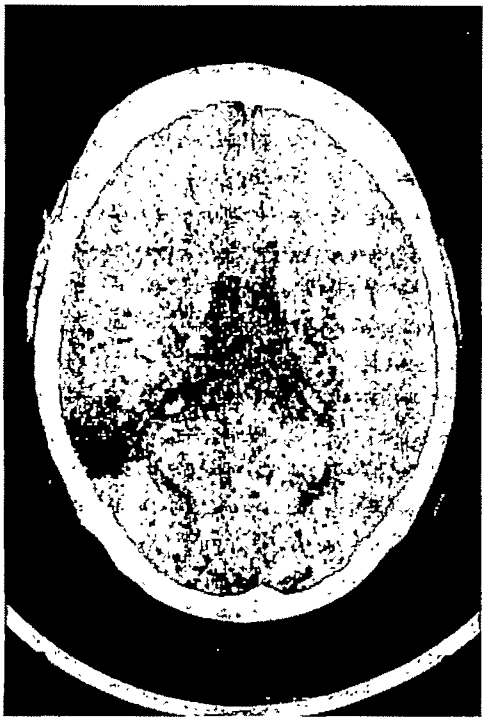


Figure 1 Axial CT scan showing an area of low density in the right posterior parietal lobe.

and status epilepticus, all of which imply an epileptic aetiology. Electroencephalographic (EEG) evidence to support such claims is variable; in cases where the EEG has been monitored during administration of propofol, evidence of epileptiform activity has not been accompanied by motor manifestations [13, 14], while EEG recordings after the events have been reported as normal [5, 12]. By late 1992, the Committee of Safety of Medicines had received 170 reports describing convulsions after the use of propofol with only a small minority of patients (14%) receiving anticonvulsants or with a past history of epilepsy. The convulsions occurred soon after administration of propofol in 69% of all patients and after a delay ranging from 1 h to 6 days in the remainder [15].

Despite the claims that propofol may have proconvulsant activity, there is a significant amount of evidence to the contrary. Propofol infusions have been shown to be effective controlling status epilepticus assessed neurophysiologically when standard treatments have failed [16–19] and are capable of inducing burst suppression in both adults and children during cardiopulmonary bypass [20, 21]. In patients undergoing surgery for intractable epilepsy, EEG recording from chronically implanted electrodes revealed no increase in seizure activity, but profound burst suppression after boluses of propofol [22], and similarly, propofol infusion did not cause increased seizure activity in patients with intractable partial epilepsy [23]. Recently, Borgeat and colleagues have shown that the excitatory movements are not accompanied by EEG changes suggestive of seizure activity [24]. Animal studies in mice [25] and rabbits [26] demonstrated that propofol was effective against both electrical and drug-induced seizures, and when used to induce anaesthesia for electroconvulsive therapy there was a significant shortening of the duration of the seizure, as assessed clinically [27–30].

A true seizure is an alteration in the CNS resulting from an electrical discharge from neurones in either cortical or subcortical tissues, evidence of which is lacking in the majority of patients described as having seizures after propofol. It has been suggested that the explanation for the origin of the seizures and opisthotonos is depression of inhibitory subcortical structures in the CNS resulting in excitatory dystonic movements and opisthotonos, characteristic of midbrain and spinal excitatory activity, respectively [31]. Subcortical centres are thought to be affected by lower concentrations of propofol for longer periods than cortical ones, which are responsible for hypnosis, as demonstrated by the observation that low doses of propofol have a direct antiemetic action [32] and reduce pruritis associated with extradural and intrathecal administration of morphine [33]. This possibly explains the greater incidence of excitatory events during the recovery phase.

A similar mechanism can be invoked in patients known to suffer from epilepsy. If a cortical focus is inhibited normally by subcortical activity, administration of propofol may result in the "release" of epileptic seizure activity in susceptible patients [34]. This is possibly the explanation for the events seen in our patient. Cerebral infarcts are a well recognized cause of seizure activity [35]. If this area was inhibited normally by subcortical activity, the seizure may have occurred as a result of depression of the inhibitory neurones before the full dose of propofol had reached the central circulation. As plasma and brain concentrations of propofol increased, the seizure abated as a result of an anticonvulsant effect. Interestingly, no convulsion was seen subsequently as propofol concentrations decreased, but this may have been masked by the concurrent use of other anaesthetic agents.

It is possible that there are two groups of patients who suffer a period of "seizure" activity after administration of propofol. The majority exhibit the motor manifestations of subcortical inhibition, without abnormal electrical discharge from any group of neurones. In these patients, the terms convulsion, seizure or epileptiform activity should be avoided, as misinterpretation could lead to the patient being labelled "epileptic" with all the attendant social and economic consequences. Perhaps dystonic or myoclonic movement would be a more accurate and less worrying description of the patient. The remainder are a small group of epileptic patients in whom a true seizure may be precipitated by administration of propofol. However, it is well known that these patients are also more susceptible to drug-induced decerebrate rigidity [36] and therefore definitive identification of the cause of such an event in a known epileptic may not be clear-cut.

Therefore, it would seem sensible to avoid the use of propofol in patients who are known to be at risk of developing seizures and in those with epilepsy if their control is poor, where anticonvulsant medication has been omitted or if they are to be discharged early after receiving propofol. However, as the present case demonstrates, the former circumstances are not always clear to either the patient or the anaesthetist, despite preoperative assessment.

Acknowledgement

We thank Dr David Hughes, consultant radiologist, for his help with arranging and reporting the CT scan.

References

1. Laycock GJA. Opisthotonos and propofol; a possible association. *Anaesthesia* 1988; **43**: 257.
2. Dingwall AE. Oculogyric crisis after day case anaesthesia. *Anaesthesia* 1987; **42**: 565.
3. Cameron AE. Opisthotonos again. *Anaesthesia* 1987; **42**: 1124.
4. Hopkins CS. Recurrent opisthotonus associated with anaesthesia. *Anaesthesia* 1988; **43**: 904.
5. Saunders PRI, Harris MNE. Opisthotonus and other unusual neurological sequelae after outpatient anaesthesia. *Anaesthesia* 1990; **45**: 552–557.
6. Paech MJ, Storey JM. Propofol and seizures. *Anaesthesia and Intensive Care* 1990; **18**: 585.
7. Collier C, Kelly K. Propofol and convulsions—the evidence mounts. *Anaesthesia and Intensive Care* 1991; **19**: 573–575.
8. Thomas JS, Boheimer NO. An isolated grand mal seizure 5 days after propofol anaesthesia. *Anaesthesia* 1991; **46**: 508.
9. Jones GW, Boykett MH, Klok M. Propofol, opisthotonus and epilepsy. *Anaesthesia* 1988; **43**: 905.
10. Modica PA, Tempelhoff R, White PF. Pro- and anticonvulsant effects of anesthetics (part I). *Anesthesia and Analgesia* 1990; **70**: 433–444.
11. Wittenstein U, Lyle DJR. Fits after alfentanil and propofol. *Anaesthesia* 1989; **44**: 532–533.
12. Shearer ES. Convulsions and propofol. *Anaesthesia* 1990; **45**: 255–256.
13. Hodkinson BP, Frith RW, Mee EW. Propofol and electroencephalogram. *Lancet* 1987; **ii**: 1518.
14. Nowack WJ, Jordan R. Propofol, seizures and generalized paraxysmal fast activity in the EEG. *Clinical Electroencephalography* 1994; **25**: 110–114.
15. Committee of Safety of Medicines. *Current problems. Propofol and delayed convulsions*, 1992; No. 35: 2.
16. Yanny, AF, Christmas D. Propofol infusions for status epilepticus. *Anaesthesia* 1988; **43**: 514.
17. Wood PR, Browne GPR, Pugh S. Propofol infusion for the treatment of status epilepticus. *Lancet* 1988; **i**: 480–481.
18. Mackenzie SJ, Kapadia F, Grant IS. Propofol infusion for control of status epilepticus. *Anaesthesia* 1990; **45**: 1043–1045.
19. Borgeat A, Wilder-Smith OHG, Jallon P, Suter PM. Propofol in the management of refractory status epilepticus: a case report. *Intensive Care Medicine* 1994; **20**: 148–149.
20. Laycock GJA, Mitchell IM, Paton RD, Donaghey SFO'B, Logan RW, Morton NS. EG burst suppression with propofol during cardiopulmonary bypass in children: a study of the haemodynamic, metabolic and endocrine effects. *British Journal of Anaesthesia* 1992; **69**: 356–362.
21. Weir DL, Laycock GJA, Alston RP. EEG suppression induced by propofol during hypothermic cardiopulmonary bypass. *Journal of Cardiothoracic Anesthesia* 1990; 4 (Suppl.): 105.
22. Ebrahim ZY, Schubert A, Van Ness P, Wolgamuth B, Awad I. The effect of propofol on the electroencephalogram of patients with epilepsy. *Anesthesia and Analgesia* 1994; **78**: 275–297.
23. Samra SK, Sneyd JR, Ross DA, Henry TR. Effects of propofol sedation on seizures and intracranially recorded epileptiform activity in patients with partial epilepsy. *Anesthesiology* 1995; **82**: 843–851.
24. Borgeat A, Wilder-Smith OHG, Despland PA, Ravussin P. Spontaneous excitatory movements during recovery from propofol anaesthesia in an infant: EEG evaluation. *British Journal of Anaesthesia* 1993; **70**: 459–461.
25. Lowson S, Gent JP, Goodchild CS. Anticonvulsant properties of propofol and thiopentone: comparison using two tests in laboratory mice. *British Journal of Anesthesia* 1990; **64**: 59–63.
26. De Riu PL, Petruzzi V, Testa C, Mulas M, Melis F, Caria MA, Mameli O. Propofol anticonvulsant activity in experimental epileptic status. *British Journal of Anaesthesia* 1992; **69**: 177–181.
27. Simpson KH, Halsall PJ, Carr CME, Stewart KG. Seizure duration after methohexitone or propofol for induction of anaesthesia for electroconvulsive therapy (ECT). *British Journal of Anaesthesia* 1987; **59**: 1323P–1324P.
28. Rampton AJ, Griffin RM, Durcan JJ, Stuart CS. Propofol and the electroconvulsive therapy. *Lancet* 1988; **i**: 296–297.
29. Rampton AJ, Griffin RM, Stuart CS, Durcan JJ, Huddy NC, Abbott MA. Comparison of methohexital and propofol for electroconvulsive therapy: effects on hemodynamic responses and seizure duration. *Anesthesiology* 1989; **70**: 412–417.
30. Dwyer R, McCaughey W, Lavery J, McCarthy G, Dundee JW. Comparison of propofol and methohexitone as anaesthetic agents for electroconvulsive therapy. *Anaesthesia* 1988; **43**: 459–462.
31. Borgeat A, Wilder-Smith OHG, Tassonyi E, Suter PM. Propofol and epilepsy: time to clarify! *Anesthesia and Analgesia* 1994; **78**: 198–199.
32. Borgeat A, Wilder-Smith OHG, Saiah M, Rifat K. Subhypnotic doses of propofol possess direct antiemetic properties. *Anesthesia and Analgesia* 1992; **74**: 539–541.
33. Borgeat A, Wilder-Smith OHG, Saiah M, Rifat K. Subhypnotic doses of propofol relieve pruritus induced by epidural and intrathecal morphine. *Anesthesiology* 1992; **76**: 510–512.
34. Bevan JC. Propofol-related convulsions. *Canadian Journal of Anaesthesia* 1993; **40**: 805–809.
35. DeLorenzo RJ. The epilepsies. In: Bradley WG, Daroff RB, Femichel GM, Marsden CD, eds. *Neurology in Clinical Practice*. Boston, USA: Butterworth-Heinemann, 1991; 1443–1477.
36. Steen PA, Michenfelder JD. Neurotoxicity and anesthetics. *Anesthesiology* 1979; **50**: 437–453.

British Journal of Anaesthesia 1996; **76**: 573–575

Airway management for patients with a tracheal bronchus

S. IKENO, H. MITSUHATA, K. SAITO, Y. HIRABAYASHI, S. AKAZAWA, H. KASUDA AND R. SHIMIZU

Summary

A tracheal bronchus is an aberrant, accessory or ectopic bronchus arising almost invariably from the right lateral wall of the trachea, causing hypoxaemia, atelectasis, or both, during anaesthesia. We describe two patients with a tracheal bronchus found before anaesthesia. One tracheal bronchus was found by tracheobronchoscopy and the other by chest x-ray. Because of recognition of the anomaly before operation, anaesthesia was uneventful in each patient. (*Br. J. Anaesth.* 1996; **76**: 573–575)

Key words

Complications, tracheal bronchus. Intubation tracheal.

Tracheal bronchus is an aberrant or accessory bronchus arising almost invariably from the right lateral wall of the trachea [1]. The incidence is reported to be approximately 0.1–3% [1–3] and is usually asymptomatic [4]. A tracheal tube can obstruct [5–7, 14] or migrate into a tracheal bronchus [7, 8], causing pulmonary atelectasis, hypoxaemia, or both. We report two patients with an ectopic tracheal bronchus that was found before operation by tracheobronchoscopy or chest x-ray.

Case reports

PATIENT NO. 1

A 55-yr-old woman was referred to our hospital for surgical treatment of carcinoma of the right middle lobe. She had undergone appendicectomy and abdominal total hysterectomy under spinal anaesthesia, but had never received general anaesthesia. Routine laboratory tests, arterial blood-gas analysis and ECG were normal. Spirometry suggested minor airway obstruction.

Bronchoscopy was performed and revealed an ectopic tracheal bronchus arising 3 cm above the carina. Chest x-ray was normal except for the tumour capacity. Tracheobronchography confirmed that the ectopic tracheal bronchus arose directly from the trachea and supplied the apical and anterior segment of the right upper lobe. The bronchus arising 4.6 cm below the carina supplied the posterior segment of the right upper lobe (fig. 1).

Lobectomy of the right middle lobe was scheduled under one-lung anesthesia with a left-sided, double-lumen endobronchial tube (BronchoCath 35Fr. Mallinckrodt Medical, St Louis, USA). Because the tracheal cuff of the tube could obstruct the tracheal bronchus when the bronchial cuff was in the left main bronchus, we examined accurately the relationship between the position of the tracheal bronchus and the tracheal cuff. The length from the peripheral edge of the tracheal cuff to the proximal edge of the bronchial cuff was 4.5 cm. The distance from the carina to the orifice of the tracheal bronchus was 3.5 cm. Therefore, when the bronchial cuff was positioned correctly, the orifice of the tracheal bronchus was located 1 cm below the tracheal cuff ensuring the patency of the tracheal bronchus.

Before induction of anaesthesia, an extradural catheter was inserted at T6–T7. After induction with thiopentone and suxamethonium, the tracheobronchus was intubated. The position of the bronchial cuff was confirmed by bronchoscopy. Anaesthesia was maintained with nitrous oxide–oxygen–sevoflurane and continuous extradural block. The operation was uneventful. The tracheobronchus was extubated after atelectasis in all lobes was excluded by chest x-ray. Her postoperative course was uneventful.

PATIENT NO. 2

A 2-yr-old girl was referred for anaesthetic assessment before burr hole irrigation for subdural empyema. She had been suffering from recurrent subdural haemorrhages from the age of 9 months, and had undergone burr hole irrigation on five occasions in another hospital.

Preoperative laboratory tests and ECG were unremarkable. Chest x-ray showed an ectopic tracheal bronchus arising about 1 cm above the carina (fig. 2). This had not been diagnosed previously. Burr hole irrigation was scheduled under general anaesthesia. Because the tracheal bronchus was identified clearly on chest x-ray, bronchoscopy was not performed before induction of anaesthesia with

---

SHIGEO IKENO, MD, HIROMASA MITSUHATA, MD, KAZUHIKO SAITO, MD, YOSHIHIRO HIRABAYASHI, MD, SATOSHI AKAZAWA, MD, HARUYUKI KASUDA, MD, REIJU SHIMIZU, MD, Department of Anesthesiology, Jichi Medical School, 3311-1 Yakushiji, Minamikawachi, Kawachi-gun, Tochigi 329-04, Japan. Accepted for publication: October 28, 1995.

Correspondence to S.I.

British Journal of Anaesthesia 1996; **76**: 573–575

Airway management for patients with a tracheal bronchus

S. IKENO, H. MITSUHATA, K. SAITO, Y. HIRABAYASHI, S. AKAZAWA, H. KASUDA AND R. SHIMIZU

Summary

A tracheal bronchus is an aberrant, accessory or ectopic bronchus arising almost invariably from the right lateral wall of the trachea, causing hypoxaemia, atelectasis, or both, during anaesthesia. We describe two patients with a tracheal bronchus found before anaesthesia. One tracheal bronchus was found by tracheobronchoscopy and the other by chest x-ray. Because of recognition of the anomaly before operation, anaesthesia was uneventful in each patient. (*Br. J. Anaesth.* 1996; **76**: 573–575)

Key words

Complications, tracheal bronchus. Intubation tracheal.

Tracheal bronchus is an aberrant or accessory bronchus arising almost invariably from the right lateral wall of the trachea [1]. The incidence is reported to be approximately 0.1–3% [1–3] and is usually asymptomatic [4]. A tracheal tube can obstruct [5–7, 14] or migrate into a tracheal bronchus [7, 8], causing pulmonary atelectasis, hypoxaemia, or both. We report two patients with an ectopic tracheal bronchus that was found before operation by tracheobronchoscopy or chest x-ray.

Case reports

PATIENT NO. 1

A 55-yr-old woman was referred to our hospital for surgical treatment of carcinoma of the right middle lobe. She had undergone appendicectomy and abdominal total hysterectomy under spinal anaesthesia, but had never received general anaesthesia. Routine laboratory tests, arterial blood-gas analysis and ECG were normal. Spirometry suggested minor airway obstruction.

Bronchoscopy was performed and revealed an ectopic tracheal bronchus arising 3 cm above the carina. Chest x-ray was normal except for the tumour capacity. Tracheobronchography confirmed that the ectopic tracheal bronchus arose directly from the trachea and supplied the apical and anterior segment of the right upper lobe. The bronchus arising 4.6 cm below the carina supplied the posterior segment of the right upper lobe (fig. 1).

Lobectomy of the right middle lobe was scheduled under one-lung anesthesia with a left-sided, double-lumen endobronchial tube (BronchoCath 35Fr. Mallinckrodt Medical, St Louis, USA). Because the tracheal cuff of the tube could obstruct the tracheal bronchus when the bronchial cuff was in the left main bronchus, we examined accurately the relationship between the position of the tracheal bronchus and the tracheal cuff. The length from the peripheral edge of the tracheal cuff to the proximal edge of the bronchial cuff was 4.5 cm. The distance from the carina to the orifice of the tracheal bronchus was 3.5 cm. Therefore, when the bronchial cuff was positioned correctly, the orifice of the tracheal bronchus was located 1 cm below the tracheal cuff ensuring the patency of the tracheal bronchus.

Before induction of anaesthesia, an extradural catheter was inserted at T6–T7. After induction with thiopentone and suxamethonium, the tracheobronchus was intubated. The position of the bronchial cuff was confirmed by bronchoscopy. Anaesthesia was maintained with nitrous oxide–oxygen–sevoflurane and continuous extradural block. The operation was uneventful. The tracheobronchus was extubated after atelectasis in all lobes was excluded by chest x-ray. Her postoperative course was uneventful.

PATIENT NO. 2

A 2-yr-old girl was referred for anaesthetic assessment before burr hole irrigation for subdural empyema. She had been suffering from recurrent subdural haemorrhages from the age of 9 months, and had undergone burr hole irrigation on five occasions in another hospital.

Preoperative laboratory tests and ECG were unremarkable. Chest x-ray showed an ectopic tracheal bronchus arising about 1 cm above the carina (fig. 2). This had not been diagnosed previously. Burr hole irrigation was scheduled under general anaesthesia. Because the tracheal bronchus was identified clearly on chest x-ray, bronchoscopy was not performed before induction of anaesthesia with

---

SHIGEO IKENO, MD, HIROMASA MITSUHATA, MD, KAZUHIKO SAITO, MD, YOSHIHIRO HIRABAYASHI, MD, SATOSHI AKAZAWA, MD, HARUYUKI KASUDA, MD, REIJU SHIMIZU, MD, Department of Anesthesiology, Jichi Medical School, 3311-1 Yakushiji, Minamikawachi, Kawachi-gun, Tochigi 329-04, Japan. Accepted for publication: October 28, 1995.

Correspondence to S.I.

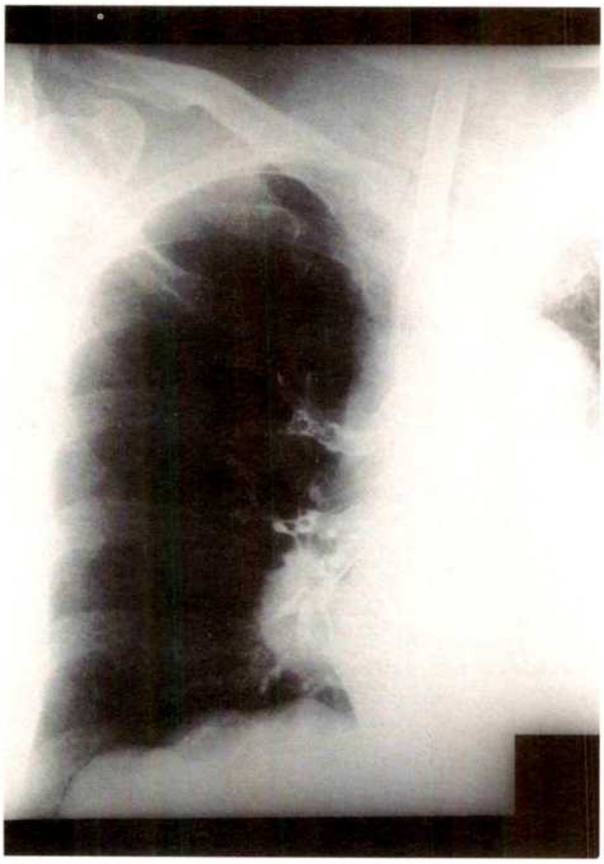


Figure 1 Tracheobronchography (patient No. 1) showing a tracheal bronchus supplying the apical and anterior segment of the right upper lobe.

nitrous oxide–oxygen–sevoflurane. After administration of suxamethonium, a tracheal tube was advanced 14 cm from the right corner of the mouth. After bilateral respiratory sounds were confirmed, tracheobronchoscopy was performed, showing that the ectopic tracheal bronchus was not obstructed. Respiratory sounds were monitored throughout and surgery was uneventfully. After chest x-ray excluded atelectasis in all lobes, the trachea was extubated. Her postoperative course was uneventful.

Discussion

In patient No. 1, we were able to perform one-lung anaesthesia safely, because we had confirmed before operation that the orifice of the tracheal bronchus was not obstructed by the double-lumen tube. In patient No. 2, the orifice of the tracheal bronchus was not obstructed with the tracheal tube, because the orifice was located near the carina.

Tracheal bronchi are associated occasionally with other congenital anomalies, including cyanotic heart disease [1], but our patients had no other anomalies. Bronchial anomalies may be reported as an incidental finding on bronchoscopy, as in patient No. 1 [1].

There are two types of tracheal bronchi: supernumerary and displaced [9]. The former, which is comparatively rare, is an accessory bronchus. A displaced bronchus arises from an abnormal position and supplies one or more segments of the upper lobe, most commonly the apical segment [4]. Although tracheal bronchi are usually reported to be asymptomatic, they may cause stridor in children. They may also be related to inflammatory conditions affecting the lung on that side, including recurrent pneumonia [4, 10], non-obstructive bronchiectasis [4, 11] and postobstructive pneumonia distal to an adenoma arising in the tracheal bronchus [4, 12]. A tracheal bronchus has been reported as high as 6 cm above the carina [4, 13]. In such patients, a tracheal tube could obstruct an ectopic tracheal bronchus [5–7, 14] or an ectopic tracheal bronchus could be intubated [7, 8], causing atelectasis, hypoxaemia, or both. Recognition of a tracheal bronchus before anaesthesia can guide airway management. In three patients reported previously, however, tracheal bronchi were found during general anaesthesia [6, 7, 14, 15], and some were identified on chest x-ray retrospectively [6]. In patient No. 2, we diagnosed a tracheal bronchus before anaesthesia on chest x-ray alone, because we were alert to the possibility.

One-lung anaesthesia in these patients may be difficult [5, 15]. In patient No. 1, we were able to perform one-lung anaesthesia safely because we had confirmed the relationship between the tracheal

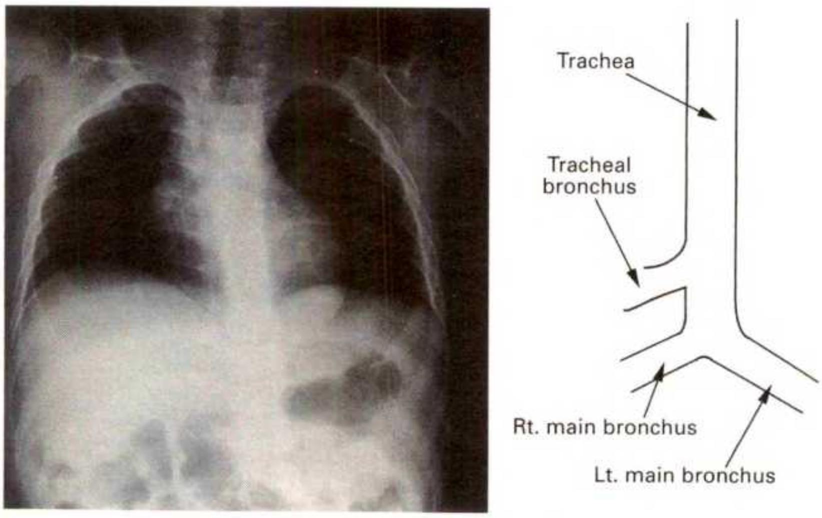


Figure 2 Chest x-ray (patient No. 2) showing an ectopic tracheal bronchus arising approximately 1 cm above the carina.

bronchus and the bronchial cuff. Bronchial blockers may be useful in some situations. In particular, for left lung surgery, a blocker in the left main bronchus enables the right lung to be ventilated effectively with a short tracheal tube.

In conclusion, chest x-ray should be observed carefully to exclude ectopic tracheal bronchus. Tracheal bronchi should be included in the differential diagnoses of airway problems, including hypoxaemia, atelectasis, or both, during anaesthesia.

References

1. McLaughlin FJ, Strieder DJ, Harris GBC, Vawter GP, Eraklis AJ. Tracheal bronchus: Association with respiratory morbidity in childhood. *Journal of Pediatrics* 1985; **106**: 751–755.
2. Le Roux BT. Anatomical abnormalities of the right upper bronchus. *Journal of Thoracic and Cardiovascular Surgery* 1962; **44**: 225–227.
3. Inada K, Kishimoto S. An anomalous tracheal bronchus to the right upper lobe. *Diseases of the Chest* 1957; **31**: 109–112.
4. Siegel MJ, Shackelford GD, Francis RS. Tracheal bronchus. *Radiology* 1979; **130**: 353–355.
5. Brodsky JB, Mark JBD. Bilateral upper lobe obstruction from a single double-lumen tube. *Anesthesiology* 1991; **74**: 1163–1164.
6. Tomoda M, Ueda W, Hasegawa T, Hirakawa M. Troubled endotracheal intubation: An adult case of anomalous tracheal bronchus. *Masui* 1992; **41**: 984–987.
7. Pribble CG, Dean JM. An unusual cause of intraoperative hypoxemia. *Journal of Clinical Anesthesia* 1994; **6**: 247–249.
8. Venkateswarlu T, Turner CJ, Carter JD, Morrow DH. The tracheal bronchus: An unusual airway problem. *Anesthesia and Analgesia* 1976; **55**: 746–747.
9. Foster-Carter AF. Broncho-pulmonary abnormalities. *British Journal of Tuberculosis and Disease of the Chest* 1946; **40**: 111–124.
10. Ferguson CF, Neuhauser EBD. Congenital absence of the lung (agenesis) and other anomalies of the tracheobronchial tree. *American Journal of Roentgenology and Radium Therapy* 1944; **52**: 459–471.
11. Schaff B, Baum G. The tracheal bronchus. *Journal of Thoracic Surgery* 1957; **33**: 282–286.
12. Epstein I. Bronchial adenoma in a supernumerary tracheal lobe. Report of an unusual case. *Journal of Thoracic Surgery* 1951; **21**: 362–369.
13. Gerson CE, Rothstein E. An anomalous tracheal bronchus to the right upper lobe. *American Review of Tuberculosis* 1951; **64**: 686–690.
14. Vredevoe LA, Brechner T, Moy P. Obstruction of anomalous tracheal bronchus with endotracheal intubation. *Anesthesiology* 1981; **55**: 581–583.
15. Stene R, Rose M, Weinger MB, Benumof JL, Harrell J. Bronchial trifurcation at the carina complicating use of a double-lumen tracheal tube. *Anesthesiology* 1994; **80**: 1162–1164.

British Journal of Anaesthesia 1996; **76**: 576P–594P

ABSTRACTS

Proceedings of the Anaesthetic Research Society

MANCHESTER MEETING

November 23–24, 1995

(The name of the author presenting the paper is shown in bold type. *Indicates non-member.)

All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

Observations on patient-controlled administration of propofol

S. J. Thorpe*, V. R. Balakrishnan* and L. B. Cook
Department of Anaesthesia, Royal Oldham Hospital

We have investigated the safety of a previously described method of patient-administered propofol [1]. This used 0.33-ml boluses of propofol 10 mg ml^{-1} infused over 6 s with no lockout. We studied 100 healthy patients (32 women, 68 men) aged 18–45 yr presenting for elective surgery.

Observations were made each min during the study. These included oxygen saturation, heart rate and an anaesthetist's assessment of the airway patency. An independent observer scored the patient's sedation using the scale in table 1 [1]. After baseline observations, patients attempted to put themselves to sleep by pressing a button on the hand-held device. The patient was deemed to have stopped pressing the button when no demands for propofol had been made for 30 s. After a set of observations had been noted, the anaesthetist took over the handset and continued to press the button until a sedation score of 6 was reached, when the study ended.

Sedation was established quickly. Only five patients were still anxious after 2 min. After 3 min no patient was still anxious and more than 70 patients had slurred speech. Men pressed the button for 312 (SD 95) s and women pressed for 247 (SD 70) s. The proportion of the total sleep dose self-administered and the dose self-administered adjusted for weight were similar in both sexes.

When they stopped pressing the button, the majority of patients were not over-sedated (table 1). However, two patients were unresponsive and nine others were over-sedated. During self-sedation there was a minor decrease in mean saturation from 97.8% to 96% ($P < 0.0001$, ANOVA). One patient desaturated to 84% transiently: no other patient's saturation fell below 90%. There were no other significant changes.

We concluded that the system studied worked well but carried too high a risk of over-sedation for unsupervised use.

Key words
Sedation, patient-controlled. Complications, overdose.

Reference

1. Cook LB, Lockwood GG, Moore CM, Whitwam JG. *Anaesthesia* 1993; 48: 1039–1044.

Table 1 Sedation scores when stopped pressing the button

Sedation score	Men	Women	Total
1. Awake and anxious	0	0	0
2. Awake not anxious	0	0	0
3. Speech slurred	36	11	47
4. Eyes closed, responds to speech	26	16	42
5. Eyes closed, responds to shaking	4	5	9
6. Unresponsive	2	0	2

Airway pressure signals during high frequency jet ventilation

E. S. Lin
Department of Anaesthesia, Glenfield Hospital Trust, Leicester

Monitoring central airway pressure (*Paw*) during high frequency jet ventilation (HFJV) is essential because of the risk of barotrauma [1]. *Paw* is monitored in practice in the central airway. However, the point at which *Paw* is sampled requires consideration because the morphology of the *Paw* waveform and its peak, mean and trough values vary with position relative to the jet [2]. Monitoring *Paw* proximal to the jet does not yield values which reflect distal airway pressures. *Paw* signals sampled 5–10 cm in front of the jet are readily accessible and lie within the tracheal or tracheostomy tube. However this region is influenced by the hydrodynamics of the injected gas. *Paw* signals recorded here have a complex waveform (fig. 1D) and their interpretation is uncertain.

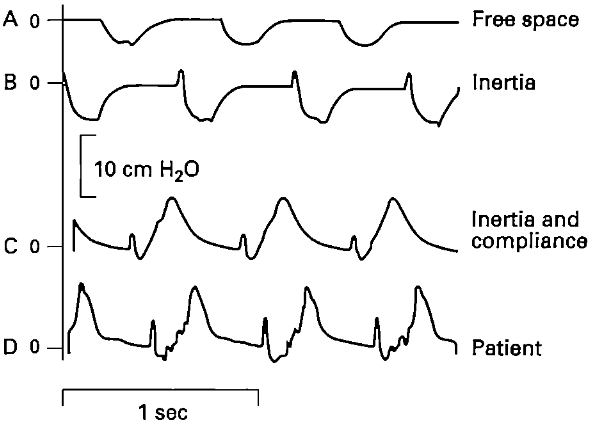


Figure 1 P5 signals during high frequency jet ventilation.

An investigation of the nearfield *Paw* signal, sampled at 5 cm (P5 signal) has been performed using a Penlon-Bromsgrove jet ventilator to inject into different load configurations. Pressure signals have been recorded with a calibrated piezoresistive transducer (Motorola MPX10DP) and signal conditioning amplifier (Analog Devices 1B131AN), using a digital storage oscilloscope (Gould 1604). Figure 1 shows P5 signals obtained during high frequency jet ventilation at 1.67 Hz (100 min^{-1}) applied to (A) free space (B) an inertia (C) an inertia and compliance in series. These results suggest that P5 signal morphology was not only related to the injected gas flow but also to the compliance and inertia of the injected load. Use of the P5 signal for monitoring airway pressure during HFJV is practical and non-invasive, and may also reflect changes in compliance and inertia of the respiratory system.

Key words
Ventilation, high frequency jet. Airway, pressure.

References

1. Egol A, Culpepper JA, Snyder JV. *Chest* 1985; **88**: 99–102.
2. Waterson CK. *Critical Care Medicine* 1984; **12**: 742–746.

Patient-controlled propofol: randomized, double-blind dose refinement

A. F. Smith*, S. J. Thorpe* and L. B. Cook
Department of Anaesthesia, Royal Oldham Hospital

Over-sedation is a danger of patient-controlled sedation [1]. We have reduced the rate of drug administration by diluting propofol to half or three quarter strength. The dose was 0.33 ml with no lockout and an infusion rate of 3.3 ml min^{-1}. These dilutions result in maximum infusion rates of 16 and 25 mg min^{-1}.

We have studied 25 healthy patients aged between 18 and 45 yr, scheduled to undergo elective operations lasting less than 30 min. Patients were allocated randomly to receive 0.5 or 0.75 % propofol in a double-blind manner. Routine non-invasive monitoring was attached, and patients were asked to try to put themselves to sleep by pressing the handset. We recorded sedation score, airway quality, heart rate and arterial oxygen saturation at 1-min intervals.

Patients were asked to say when they first noticed any sedative effect. The time of onset of slurred speech was noted. In addition, patients were shown three objects—before starting, at 2.5 and at 4.5 min. When the patient became sedated enough so as not to press the button for 30 s, we took over the handset and continued giving propofol using the pump until the patient was unresponsive. Postoperatively, recall of the objects shown was tested. The data were analysed using the unpaired two tailed *t*-test or chi-square test as appropriate. Table 2 shows the results.

Table 2 Mean (SD) values for sedation times and amnesia for the two groups

	0.5 % Propofol group ($n = 9$)	0.75 % Propofol group ($n = 16$)	*P* value
Notices effect (min)	2.8 (2.1)	1.7 (0.8)	NS
Slurred speech (min)	5.7 (1.9)	3.9 (1.3)	< 0.05
Time to sedation (min)	6.7 (1.8)	4.5 (1.4)	< 0.01
Amnesia at 2.5 min	0 %	17 %	NS
Amnesia at 4.5 min	0 %	43 %	< 0.05
Over-sedated	0	0	—

We concluded that propofol at 16 mg min^{-1} takes too long to produce amnesia and sedation to be useful in clinical practice. A maximum infusion rate of 25 mg min^{-1} may represent an acceptable compromise between speed of onset and risk of over-sedation.

Key words
Sedation, patient-controlled. Anaesthetics i.v., propofol. Complications, overdose.

Reference

1. Thorpe SJ, Balakrishnan VR, Cook LB. *British Journal of Anaesthesia* 1996; **76**: 576P.

Auditory evoked responses, median frequency and 95 % spectral edge during anaesthesia with desflurane and nitrous oxide

S. K. Pal*, R. Sharpe*, D. Nathwani* and D. E. F. Newton
Academic Department of Anaesthesia, St Mary's Hospital Medical School, Northwick Park Hospital, Harrow

Desflurane has rapid onset and emergence from anaesthesia. In paralysed patients a reliable means of monitoring light anaesthesia is, therefore, more important than with other volatile agents. We compared auditory evoked responses (AER) with EEG power spectral analysis in 12 patients. The study was approved by the Harrow Research Ethics Committee. Premedication was with morphine 10 mg and atropine 0.4 mg and anaesthesia was induced by inhalation of desflurane in 67 % nitrous oxide in oxygen. Tracheal intubation was followed by vecuronium 0.1 mg kg^{-1} given by infusion to produce two train-of-four responses. In four 10-min periods, the patients received 1.5, 3 or 6 % desflurane in random order. In the fourth period the previous concentration was repeated, ensuring that every dose followed every other dose including itself equally often. This eliminates carryover effects while retaining the advantage of a within-patient study.

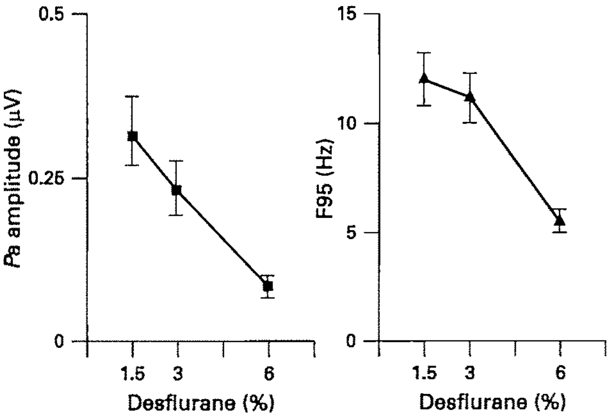


Figure 2 *Pa* amplitude of the AER and the F95 (95 % confidence limits of between-patient data).

A calibrated Datex Ultima measured end-expiratory gas concentrations, and the $P\mathrm{E}'_{CO_2}$ was maintained at 4.5–5 kPa. The AER, median frequency (F50) and 95 % spectral edge (F95) of the EEG were recorded for the last 2.5 min of each period, using specially designed equipment [1].

ANOVA was performed on the log of *Pa* and Nb amplitudes and latencies and on the F50 and F95 of the within-patient data. There was a highly significant effect of dose for all variables (fig. 2) (*Pa* and Nb amplitude $P < 0.001$; *Pa* and Nb latencies $P \leqslant 0.002$; F59 and F95 $P < 0.001$). Burst suppression was not observed.

Rampil [2] investigated desflurane in nitrous oxide at a higher range of doses (6 %–15 %), and although at 6 % his values for F50 and F95 (4.2 Hz and 17.1 Hz) were greater, this can be accounted for by premedication. At low concentrations the AER showed a greater linearity with dose than the EEG variables, and may be better at monitoring light anaesthesia in the paralysed patient.

Key words
Anaesthetics gases, nitrous oxide. Anaesthetics volatile, desflurane. Brain, evoked potentials. Brain, electroencephalography.

References

1. Jordan C, Weller C, Thornton C, Newton DEF. *Journal of Medical Engineering & Technology* 1995; **19**: 77–79.
2. Rampil S, Lockhart SH, Eger EI, Yasuda N, Weiskopf RB, Calahan MK. *Anesthesiology* 1991; **74**: 434–439.

Evaluation of bispectral index as an objective sedation score in the intensive care unit

A. J. Pearson, C. J. D. Pomfrett, B. R. H. Doran and B. J. Pollard
University Department of Anaesthesia, Manchester Royal Infirmary

Bispectral analysis is an advanced EEG signal processing technique which tracks both linear and non-linear changes in signals to enable subtle changes in electrical brain activity to be quantified. The bispectral index (bsi) is a numerical display of the overall bispectral properties (power, frequency and phase) generated by a sophisticated algorithm. Previous work has shown a correlation between bispectral analysis and patient movement at skin incision during anaesthesia [1, 2], but as yet little work has been published to show the reliability of bispectral analysis for objectively measuring depth of sedation in the intensive care unit (ICU).

Five intensive care patients, aged 30–77 yr, were studied. All patients were receiving sedation to ensure compliance with mechanical ventilation. A modified Ramsey score was used by the ICU nursing staff to assess the level of sedation for each patient before EEG recording. The bsi was recorded (using the Aspect A1000) at 15-min intervals on each patient for a 1-h period, two or three times a day. During EEG recording normal ICU routine was allowed to continue in order to have a true reflection of the effects on the indices. The data were examined for any correlation between sedation scores and bsi.

The overall range of the bsi was 17–96. The mean bsi for patients with a sedation score of 4 was 66.8, for a score of 5 was 63.5 and for a score of 6 was 34.6. Using the Wilcoxon signed rank test there was no significant difference in bsi in patients with a sedation score of 4 and 5 ($P = 0.12$) but there was a significant difference between the patients with scores of 4 and 5 and those with a score of 6 ($P = 0.02$ and $P = 0.02$).

Increases in bsi were observed when patients were disturbed either for nursing intervention or physiotherapy, but in all cases no alteration in the patients sedation score was evident.

Key words
Brain, electroencephalography. Sedation.

Acknowledgement

We thank Spacelabs/Aspect Medical for the loan of the Aspect A1000.

References

1. Kearse AL, Manberg P, Chaumann N, du Bras F. *Anesthesiology* 1994; 81: 1365–1370.
2. Sebel PS, Rampil S, Cork R. *Anesthesiology* 1993; 79s: 3A.

Evoked EMG response during inhalation of a sub-anaesthetic concentration of isoflurane

S. L. Polhill* and D. C. Smith
Department of Anaesthesia, Southampton General Hospital, Southampton

Failure to maintain the pre-block control response is the major limit to the usefulness of the evoked EMG for monitoring neuromuscular transmission during anaesthesia. The EMG response does not decrease in awake volunteers [1]. Sub-anaesthetic concentrations of isoflurane have been given to volunteers [2] and used for long-term sedation in the intensive therapy unit [3], but the effect on neuromuscular transmission has not been studied.

We studied 15 volunteers who were free of neuromuscular disease and who were not taking drugs known to modify neuromuscular transmission. Neuromuscular transmission was measured with a Relaxograph and Medicotest Blue Sensor P-00-S electrodes. Supramaximal stimulation of the ulnar nerve at the wrist produced a response recorded over the belly of the first dorsal interosseous muscle, with the indifferent electrode on the proximal phalanx of the first finger. The ground electrode was placed over the median nerve at the distal wrist crease. The arm was abducted to 45°, supinated and placed on an armboard with 30° flexion at the elbow. The fingers were strapped flat onto the board with adhesive tape. The subjects were asked to relax completely before the study started. The Relaxograph was calibrated to the 100 % transmission reference with the volunteers breathing room air, and the EMG response was recorded every 20 s for 25 min. After 2 min with a stable T1 response, the volunteers started to breathe 0.2 % isoflurane in oxygen, from a calibrated vaporizer, via a Mapleson A breathing system with a fresh gas flow of 8 litre min^{-1}. After 25 min the study was stopped and the Relaxograph was recalibrated.

Verbal contact was maintained with the volunteers at all times; although most felt light-headed, none lost consciousness. The T1 response of the EMG remained at 100 (5)% in 10 of the 15 subjects. Of the other five subjects, in three cases the T1 response decreased below 95 % of the control response, while in two cases the response increased to greater than 105 % of control. However, in no subject did the T1 response deviate more than ±10 % from the control value. The supramaximal stimulus current at recalibration was identical to that at initial calibration in all subjects.

The changes in the control response of the evoked EMG in this study were not clinically significant, and were similar to those seen in awake volunteers [1].

Key words
Neuromuscular transmission. Neuromuscular block: measurement of response. Measurement techniques: electromyography.

References

1. Fisher W, Smith DC. *British Journal of Anaesthesia* 1994; 73: 261.
2. Pearsall FJ, Asbury AJ. *British Journal of Anaesthesia* 1993; 71: 370.
3. Spencer EM, Willatts SM, Prys-Roberts C. *British Journal of Anaesthesia* 1990; 65: 574.

Magnetic resonance imaging of the superior vena cava during spontaneous respiration with continuous positive airway pressure via a facemask in normal subjects

A. H. Mayor*, P. Hughes*, I. Ryder* and J. R. Sneyd
Departments of Anaesthesia and Imaging, Derriford Hospital, Plymouth

Although there are beneficial effects of continuous positive airway pressure (CPAP) in respiratory failure and upper airway obstruction, the increase in intrathoracic pressure may reduce cardiac output, by increasing resistance to venous return and/or impairing ventricular function. Previous studies with magnetic resonance imaging (MRI) have looked at the effect of positive end expiratory pressure (PEEP) on atrial and ventricular cardiac volumes in ventilated subjects [1]. The purpose of the present study was to determine the effect of facemask CPAP on superior vena cava (SVC) cross-sectional area and left and right ventricular size and shape, in an attempt to clarify the mechanism of decreased cardiac output.

Five healthy male volunteers were studied breathing spontaneously for four 30-min periods with 0, 7.5, 15 and 0 cm H_2O CPAP via a tight fitting facemask. MRI imaging consisted of cardiac gated T2-weighted axial images of the SVC and short axis images of the ventricles. Short axis imaging planes were prescribed separately for each different CPAP level to avoid errors as a result of cardiac rotation and lifting. Measurements on SVC and left and right ventricular cross-sectional area were obtained by manually tracing the regions of interest on sequential scans using a pre-program data package averaging two independent estimations at each level. Heart rate and non-invasive blood measurements were made during each study. So far SVC diameter data have undergone analysis. Statistical analysis was by ANOVA.

SVC cross-section was significantly reduced throughout the cardiac cycle by 15, but not by 7.5 cm H_2O CPAP, $P < 0.005$ ANOVA (fig. 3).

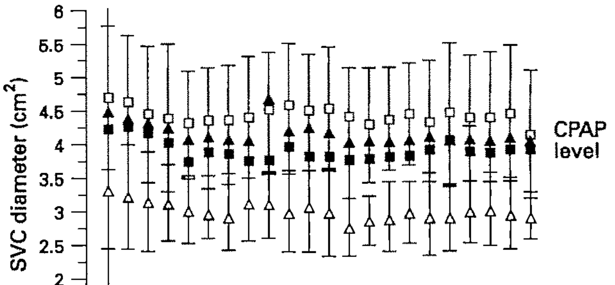


Figure 3 The effect of continuous positive airway pressure (CPAP) on superior vena cava (SVC) diameter during spontaneous respiration, $n = 5$, data are means (SD). Some error bars have been omitted for clarity. (□) 0 cm H_2O, (■) 7.5 cm H_2O, (△) 15 cm H_2O, (▲) 0′ cm H_2O.

Key words
Measurement techniques, nuclear magnetic resonance. Airway, pressure.

Reference

1. Leithner C. *Critical Care Medicine* 1994; 22: 426–432.

Post-tetanic constant stimulus train patterns during neuromuscular block with atracurium and vecuronium

A. Bryan, B. J. Pollard, M. A. Keegan* and I. T. Campbell
University Department Anaesthesia, Manchester Royal Infirmary, Manchester

The response to varying frequency (de-crescendo) trains of stimuli given 1 s after tetanic stimulation of 50 Hz for 5 s has been previously reported [1]. This study examined the response to constant frequency post-tetanic trains of stimuli.

The electromyographic data acquisition system was custom built using a 386 PC, an analogue to digital converter, isolated pre-amplifier and programmable stimulator [2]. The stimulator was programmed to deliver trains of constant current, supramaximal stimulus pulses of width 0.2 ms according to a predefined suite of patterns. The pulse train patterns each consisted of a single twitch, a 15-s delay, a tetanic stimulus of 50 Hz for 5 s, a 1-s delay and a constant frequency train. The constant frequency trains were CT1 (2 Hz), CT2 (4 Hz), CT3 (6 Hz), CT4 (8 Hz) and CT5 (10 Hz). The electromyographic response of the adductor pollicis to ulnar stimulation was recorded using surface electrodes to monitor neuromuscular block and the data were stored for off-line analysis.

Anaesthesia was induced using thiopentone and maintained using nitrous oxide–oxygen–enflurane with fentanyl as required. The data acquisition system was calibrated and either atracurium 0.4 mg kg^{-1} ($n = 5$) or vecuronium 0.07 mg kg^{-1} ($n = 5$) was given. The trachea was intubated and ventilation controlled. End-tidal CO_2 was maintained at 35–40 mm Hg. Trains of stimuli were administered at 5-min intervals and neuromuscular block maintained using increments of the same agent as for intubation. At the end of the procedure residual block was antagonized using neostigmine and glycopyrronium.

The ratio of the evoked compound action potential peak-to-peak response of the single twitch (To) and of each response (Tn) of the constant series for train CT1 is shown in figure 4.

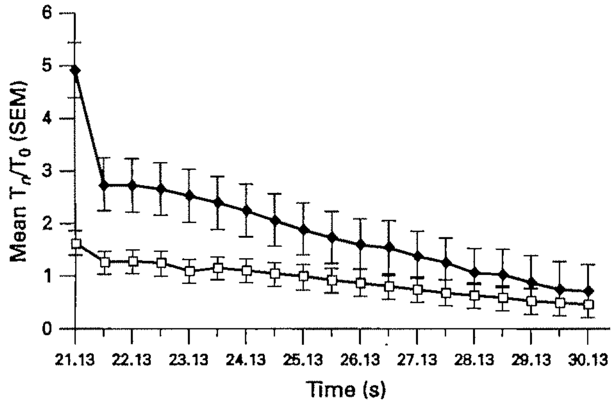


Figure 4 Mean response to train CT1.

There was a significant difference in the area under the curve for the atracurium group compared with the vecuronium group for train CT1 ($P < 0.05$, two sample t-test) and for the mean value of the observations for trains CT2 and CT5. This pattern of response is similar to the standard post-tetanic count response to 1.0-Hz stimulation with the inherent effect of fade from atracurium and vecuronium and differs from that seen with varying frequency pulse trains.

Key words
Measurement techniques, electromyography. Neuromuscular block, vecuronium. Neuromuscular block, atracurium.

References

1. Pollard BJ, Bryan A, Willard T. *British Journal of Anaesthesia* 1994; 73: 716P.
2. Willard T, Bryan A, Pollard BJ. *Journal of Physiology* 1995; 483P.

Effect of stimulation rate on force of contraction in partially paralysed rat phrenic nerve hemidiaphragm preparations

K. Richards*, A. J. England and A. Feldman
The Magill Department of Anaesthesia, Chelsea and Westminster Hospital, London and The John Hammond Department of Anaesthesia, East Surrey Hospital, Redhill

Bowman [1] has postulated that presynaptic receptors augment acetylcholine release at the neuromuscular junction during high rates of stimulation. We have attempted to quantify the effect of drug activity on the putative pre- and post-synaptic receptors by using fast and slow rates of indirect stimulation.

Wistar rat phrenic nerve hemidiaphragm preparations were suspended in Kreb's solution maintained at 37 °C. They were pretensioned to 8 *g* and, after stabilization, indirect supramaximal square wave stimuli were applied. A series of experiments was performed using α-bungarotoxin, an agent believed to bind preferentially to the post-synaptic receptor [2], hexamethonium, an agent suspected of having marked presynaptic receptor activity [1, 3], vecuronium and rocuronium. A dose of drug previously demonstrated to give about 10% twitch height depression (THD) during 0.1-Hz rates of stimulation was added to the tissue bath and the THD allowed to stabilize. Without washing out the neuromuscular blocking agent the preparation was then stimulated at rates of 0.2 Hz, 0.5 Hz, 1 Hz and 2 Hz and the response recorded. The mean percentage THD after 200 twitches was calculated for each agent and at each rate of stimulation. The relationship between percentage THD and rate of stimulation (and the standard deviation of the residuals from the line) for each agent was calculated by linear regression and comparison between the groups at each rate of stimulation was by analysis of variance.

Twenty-two rats were used during this series of experiments giving 35 data points for α-bungarotoxin, 52 for hexamethonium, 52 for vecuronium and 38 for rocuronium. The results are displayed in figure 5.

The slopes of the regression lines were −6.9% Hz^{-1} (8.0) for α-bungarotoxin, 28.4% Hz^{-1} (15.9) for hexamethonium, 15.5% Hz^{-1} (9.1) for vecuronium and 31.9% Hz^{-1} (13.0) for rocuronium.

There was no significant difference between any groups at 0.2-Hz stimulation rates ($P > 0.05$ for all comparisons).

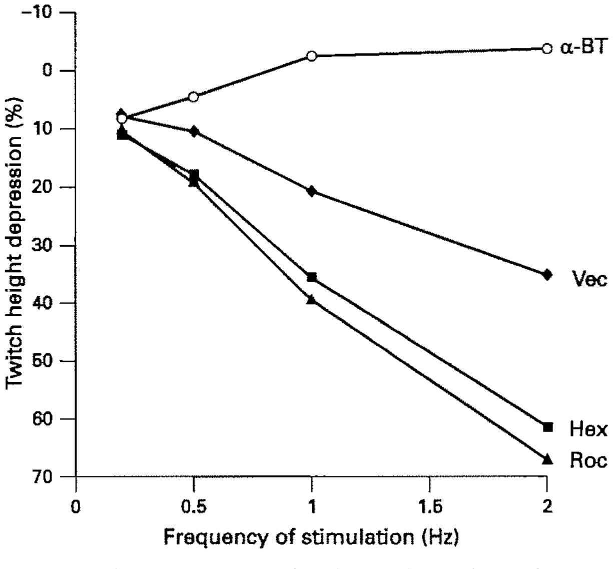


Figure 5 Mean percentage twitch height depression and frequency of stimulation for four neuromuscular blocking agents.

There was no significant difference between hexamethonium and rocuronium at any frequency of stimulation ($P > 0.05$ for all comparisons).

At 0.5 Hz hexamethonium and rocuronium produced more THD than α-bungarotoxin ($P < 0.001$ and $P < 0.001$); and rocuronium produced more THD than vecuronium ($P < 0.05$).

At 1 Hz hexamethonium and rocuronium produced more THD than α-bungarotoxin ($P < 0.001$ and $P < 0.001$) and vecuronium ($P < 0.05$ and $P < 0.05$). Vecuronium produced more THD than α-bungarotoxin ($P < 0.01$).

At 2 Hz hexamethonium and rocuronium produced more THD than α-bungarotoxin ($P < 0.001$ and $P < 0.001$) and vecuronium ($P < 0.01$ and $P < 0.01$). Vecuronium produced more THD than α-bungarotoxin ($P < 0.01$).

The mechanisms underlying α-bungarotoxin and hexamethonium neuromuscular block can be readily differentiated using a small dose of drug by the degree of THD after 200 twitches at frequencies of 1 or 2 Hz. Rocuronium had a similar response to hexamethonium suggesting a presynaptic site of action, but vecuronium lies between hexamethonium and α-bungarotoxin, suggesting a mixed pre- and post-synaptic effect.

Key words
Site of action; presynaptic, postsynaptic. Neuromuscular block, α-bungarotoxin. Neuromuscular block, hexamethonium. Neuromuscular block, vecuronium. Neuromuscular block, Rat. Nerve. Receptors, presynaptic, Receptors, postsynaptic, rocuronium.

References

1. Bowman WC. *Anesthesia and Analgesia* 1980; **59**: 935–943.
2. Lee C, Chen D, Katz RL. *Canadian Anaesthetic Society Journal* 1977; **24**: 212–219.
3. Gibb AJ, Marshall IG. *British Journal of Pharmacology* 1986; **89**: 619–624.

Onset time of neuromuscular block is determined by the pharmacokinetics of the blocking drug

A. M. Beaufort*, V. Nigrovic, J. H. Proost*
and J. M. K. H. Wierda

Research Group for Experimental Anesthesiology and Clinical Pharmacology, University of Groningen, Groningen, the Netherlands, Department of Anesthesiology, Medical College of Ohio, Toledo, USA, and Department of Pharmacokinetics and Drug Delivery, University Centre for Pharmacy, Groningen, the Netherlands

Previous reports document that a neuromuscular blocking agent of low potency has a short onset time of submaximal neuromuscular block [1, 2]. The ED_{50}, the i.v. bolus dose of a neuromuscular blocking drug that produces a half-maximal neuromuscular block, is determined by the drug's EC_{50}, the concentration at the site of action that produces a half-maximal neuromuscular block and by its pharmacokinetics. The question we asked was whether the onset time is determined by the agent's EC_{50} or by its pharmacokinetics.

Assuming that inhibition of the enzymic degradation of a neuromuscular blocking agent in plasma does not alter the drug's EC_{50} but only decreases the rate of disappearance of the agent from plasma, its potency—reflected in a lower equi-effective dose—will be increased. It follows that, after inhibition of the enzymic degradation, the onset time will be unaltered were it dependent on EC_{50} and prolonged were it dependent on pharmacokinetics.

Twenty-one pigs were anaesthetized and prepared for measuring the indirectly elicited contractions of the tibialis anterior muscle (supramaximal, single twitch, 0.1 Hz). In 20 pigs the ED_{70} and the onset time (time to peak submaximal neuromuscular block) were determined for either suxamethonium ($n = 10$) or mivacurium ($n = 10$). Thereafter, in 10 of the pigs an inhibitor of plasma cholinesterase (TIPPA) 2.6 mg kg^{-1} was injected i.v. and the ED_{70} and onset time were reassessed. In each pig, inhibition of plasma cholinesterase was documented by measuring its activity in plasma. To assess any influence of the inhibitor on junctional acetylcholinesterase, a continuous infusion of vecuronium maintained, in a separate pig, a 50% neuromuscular block during which the inhibitor was administered.

The inhibitor reduced the activity of plasma cholinesterase by 92.7 (SD 4.1)% (suxamethonium) and by 89.9 (2.2)% (mivacurium). Inhibition of plasma cholinesterase reduced the ED_{70} of suxamethonium from 900 (400–1000) (median (range)) to 150 (135–150) μg kg^{-1} and prolonged the onset time from 40 (20–45) to 131 (114–166) s. Similarly, inhibition of plasma cholinesterase reduced the ED_{70} of mivacurium from 100 (80–150) to 35 (20–50 μg kg^{-1} and prolonged the onset time from 52 (40–59) to 105 (90–125) s. Inhibition of plasma cholinesterase did not alter the vecuronium-induced 50% neuromuscular block, whereas neostigmine decreased the block.

Inhibition of the enzymic degradation of suxamethonium and mivacurium in plasma prolonged the onset time of submaximal neuromuscular block. Since inhibition of the enzymic degradation has no influence on a vecuronium-induced 50% neuromuscular block, we concluded that the onset time of submaximal neuromuscular block is determined by the pharmacokinetics of the blocking agent.

Key words
Neuromuscular block, suxamethonium. Neuromuscular block, mivacurium. Pigs.

References

1. Bowman WC, Roger ZW, Houston J, Marshall RJ, McIndemon I. *Anesthesiology* 1988; **69**: 57–62.
2. Wierda JMKH, Proost JH. *European Journal of Anaesthesiology* 1995; **12** (S11): 45–55.

Modelling the interaction of two neuromuscular blocking agents: generation of an additive or a supra-additive neuromuscular block

V. Nigrovic, H. Mellinghoff* and W. Buzello
Anaesthesiology Clinic, University of Cologne, Germany

It has been repeatedly shown that two non-depolarizing neuromuscular blocking agents administered in equi-effective doses produce either a neuromuscular block of a size expected from the sum of the doses (additive effect) or a larger neuromuscular block (supra-additive effect). Generation of an additive or a supra-additive neuromuscular block by two neuromuscular blocking agents has not been modelled previously.

The nicotinic receptor at the end plate has two binding sites for acetylcholine or the neuromuscular blocking agents. Some neuromuscular blocking agents bind preferably to the one site while others bind to the other. For a given site, the ratio of the rate constant for dissociation, k_{dissoc}, to the rate constant for binding, k_{assoc}, defines the equilibrium dissociation constant, K_D, of that neuromuscular blocking agent for that site. A low value for K_D defines a high affinity (strong binding). We postulated that if the first neuromuscular blocking agent forms a strong complex with the first site, a weak one with the second, and a third by binding to both sites, then the second neuromuscular blocking agent might form either similar complexes or a weak complex with the first site, a strong one with the second site, and a third by binding to both sites. We labelled the latter pattern the inverse pattern of affinities. When two neuromuscular blocking agents are present together, eight types of complexes are formed. If the neuromuscular blocking agents display an inverse pattern of affinities then the two additional complexes contain the neuromuscular blocking agents bound either both strongly or both weakly. We equated the concentrations of the neuromuscular blocking agents in the synaptic clefts with their concentrations in the interstitial space of muscle and assumed that only the free neuromuscular blocking agent is available for back-diffusion into the plasma and for binding to the receptors. The rate of change of the concentration for each of the eight complexes was expressed as a difference between the corresponding rates of formation and dissociation. The concentration of the free receptors was defined as the difference between the total receptor concentration ($[R]_{tot} = 4.10^{-9}$ mol $litre^{-1}$, two binding sites per receptor) and the sum of the concentrations of all the complexes. For all neuromuscular blocking agents k_{assoc} was assigned an identical value (4×10^8 min^{-1} mol $litre^{-1}$). We considered two conditions: (i) the neuromuscular blocking agents bind with high affinity to the same receptor site, or (ii) neuromuscular blocking agents show an inverse pattern of affinities, i.e. one neuromuscular blocking agent binds strongly to the first and the other to the second site.

The simulations demonstrated that when the two neuromuscular blocking agents bind to the same site with high affinity, the resulting neuromuscular block is additive. When the neuromuscular blocking agents were assigned an inverse pattern of affinities, the neuromuscular block was enhanced, i.e. supra-additive. The supra-additive neuromuscular block was less pronounced for two neuromuscular blocking agents with vastly different pharmacokinetic properties and could be simulated with neuromuscular blocking agents administered simultaneously or in sequence (the second neuromuscular blocking agent after a partial recovery of the neuromuscular block produced by the first neuromuscular blocking agent). The supra-additive effect was larger proportional to the ratio of affinities of the neuromuscular blocking agents for the two sites.

The proposed model simulated the clinical results. We propose that neuromuscular blocking agents belonging to different chemical groups (isoquinoline or aminosteroid) displayed an inverse pattern of affinities for the two binding sites and, when present together, produced a supra-additive neuromuscular block with a preponderance of the strong complexes (both neuromuscular blocking agents bound to their sites of high affinity).

Key words
Neuromuscular block, drug interaction. Pharmacodynamics.

Acknowledgement

VN is a guest professor supported by the University zu Koeln.

Infertility among female hospital doctors in the UK

N. J. MARAN*, R. P. KNILL-JONES AND A. A. SPENCE*
University Department of Anaesthetics, Royal Infirmary, Edinburgh and Department of Public Health, University of Glasgow

An increased incidence of involuntary infertility has been noted in studies of female anaesthetists [1, 2]. A more recent study has shown decreased fertility in female dental surgical assistants exposed to nitrous oxide [3].

A prospective postal survey of the health of all female doctors in the UK was carried out between 1977 and 1985. Annual mailings requested details of occupation, work practice, lifestyle, medical and obstetric history as well as some personal details. The principal method of contraception used in each quarter was recorded and any woman recording 8 or more consecutive quarters of no contraception was regarded as having 2 yr or more of infertility. Further details were requested from this group in a follow-up questionnaire.

Infertility was classified as primary or secondary and where infertility was confirmed (including those who had been investigated and no problem found), infertility was termed "pure". A further restricted analysis for the years after 1979 was carried out as more details were made available by a second questionnaire.

Each variable was analysed independently (chi-square) and thereafter all significant variables and all occupational variables were analysed using logistic regression to eliminate the effect of confounding variables.

A total of 913 women recorded 2 yr or more of apparent infertility. Thirty-two stated that their infertility was "not a problem" and were therefore excluded from analysis. In 138 cases, there was doubt as to the accuracy of coding, this group being significantly younger than other women who reported infertility ($P < 0.0001$). Data were analysed both with and without this group. The overall incidence of 2-yr infertility among the female doctors was 6.7–8.3%.

After logistic regression, the only significant variable to affect all groups was increasing maternal age and ethnicity (non-white women reporting more infertility). In the pre-1979 analysis, the only significant occupational variables were that those who worked a rota less arduous than a 1 in 6 reported more infertility. In infertility reported after 1979, however, there appeared to be a small increase in reporting with increasing number of sessions worked each week.

We found no evidence that female anaesthetists have any increased risk of infertility.

Key words
Infertility. Anaesthetist, risks.

Acknowledgement

This study was supported by grants from the MRC and Department of Health.

References

1. Knill-Jones RP, Rodrigues LV, Moir DD. *Lancet* 1972; 1: 1326–1328.
2. Tomlin PJ. *British Medical Journal* 1979; 1: 779–783.
3. Rowland AS, Baird DD, Weinberg CR. *New England Journal of Medicine* 1992; 327: 993–997.

Patient attitudes to perioperative suppository administration for postoperative analgesia

M. CARROLL*, F. DAY*, A. HENNESSY* AND C. COONEY*
Department of Anaesthesia, Neath Hospital, Dublin

Diclofenac is effective for postoperative analgesia when administered orally, rectally or by i.m. injection. I.m. injection may be painful [1], yet recent controversy surrounding the use of suppositories has led to concern regarding its rectal administration without informed consent [2].

Four hundred surgical patients were asked to express their preference for i.m. or rectal diclofenac for postoperative pain relief; 82% of patients chose an i.m. injection (85.6% males, 77.5% females, $P < 0.05$). The mean age of men who chose an i.m. injection was 45.2 yr, compared with 49.5 yr for those who chose a suppository. This was not statistically significant. The mean age of females choosing an i.m. injection was 47.8 yr compared with 51.5 yr for those choosing a suppository ($P = 0.13$). Males choosing a suppository were more likely to belong to a higher socioeconomic group ($P < 0.005$). No such difference in socioeconomic profile was observed for females. Females choosing a suppository were more likely to be married and have children ($P < 0.01$). When the possibility of discomfort at the injection site was explained, 22.6% of patients chose a suppository instead (24.7% males, 19.6% females, $P > 0.05$). Females who changed their mind were more likely to belong to a higher socioeconomic group and to be married ($P < 0.05$): 27% of patients choosing an i.m. injection expressed concern that a suppository might be inserted without consent; 11% of patients who chose a suppository expressed similar concern.

Key words
Analgesia, postoperative. Analgesics non-opioid, diclofenac.

References

1. Serratrice G. *Tribune Medicine* 1982; **46**: 43–48.
2. Mitchell J. *British Medical Journal* 1995; **310**: 43–48.

A novel fibreoptic pressure transducer system for the upper airway

C. SECKER*, C. D. HANNING, P. GOODYER*, J. FOTHERGILL* AND N. B. JONES*
Departments of Anaesthesia and Engineering, University of Leicester

A novel fibreoptic pressure transducer system (FPTS) has been developed for investigation of the upper airway after anaesthesia and during sleep.

The FPTS comprises a flexible catheter, od 3 mm, containing seven fibreoptic pressure transducers [1]. One is placed at the tip and the others spaced at 20-mm intervals 200–300 mm from the tip. The catheter is covered with a flexible latex membrane which is sealed between transducers to form a "balloon" at each measurement site. The FPTS was calibrated before use by placing it in an airtight chamber and subjecting it to pressures of ±10 cm H_2O measured with an aneroid gauge. Analogue signals from the FPTS were collected using an IMS2000 Cardio Respiratory Sleep System with CARDAS software on a notebook computer (Acer 486) and subsequently exported as ASCII files to a spreadsheet

(Microsoft Excel). The FPTS was passed nasally in eight anaesthetized patients undergoing peripheral surgery and guided into the oesophagus. It was placed so that the distal transducer was mid-oesophagus and the remainder arrayed from posterior nasopharynx to hypopharynx with the second transducer immediately posterior to the soft palate. Position was confirmed by laryngoscopy. After at least 10 min for equilibration, recordings were begun from discontinuation of anaesthesia and return of spontaneous breathing until recovery of full consciousness when the FPTS was removed. Patients were under the care of a trained recovery nurse and were monitored clinically and with pulse oximetry. She was instructed to manage the cases according to usual practice, supporting the airway as she felt necessary.

Satisfactory recordings were obtained in all patients. Several patterns of pressure waveforms were seen. During unobstructed normal breathing, synchronous pressure changes were seen at all sites, the pressure change increasing from proximal to distal. During complete obstruction, increased inspiratory pressure changes were seen distal to the presumed level of obstruction, with no pressure changes above that level. At the presumed level of obstruction, several patterns were seen. The most usual was an inverted pressure waveform with pressure increasing during inspiration. The same pattern was seen during partial obstruction and was usually associated with a waveform suggestive of flow limitation in the distal transducers. This latter waveform was also associated with a reduced, in-phase pressure waveform at the presumed site of obstruction. Snoring was seen as a high frequency pattern superimposed on the pressure waveform.

We hypothesized that the differing pressure changes at the site of obstruction may be explained by pressure on the "balloon" of each transducer. The subatmospheric collapsing force during inspiration was countered by an increase in airway dilator muscle activity. In the awake state this resulted in an increased airway calibre and the transducer reflected intraluminal pressure. In the presence of anaesthetic agents the dilator activity was reduced and airway calibre reduced with inspiration, applying wall pressure to the "balloon". As airway calibre reduced, the wall pressure initially balanced and then exceeded intraluminal pressure giving the reduced amplitude and out-of-phase pressure changes.

The results suggested that airway narrowing may be progressive and is not always associated with snoring. The FPTS may be of value in future investigations of the upper airway.

Key words

Airway, complications. Airway, calibre.

Acknowledgement

The project was supported by a grant from the British Lung Foundation.

Reference

1. Goodyer P, Fothergill J, Jones NB, Hanning CD. *IEEE Transactions* 1995 (in press.)

Economy during induction of anaesthesia: a comparison of desflurane with isoflurane via a circle system

S. K. PAL*, Z. ZYCH*, R. RAJENDRAM* AND D. C. WHITE
Department of Anaesthetics, Princess Alexandra Hospital, Harlow, Essex

The use of isoflurane and recently introduced desflurane has increased anaesthetic cost. Renewed interest in low-flow anaesthesia with carbon dioxide absorption has made possible considerable cost savings during maintenance of anaesthesia. However, no attempt has been made to reduce the cost during induction and early stages of anaesthesia because it is generally believed that it is difficult to close the circuit from the start of the anaesthetic. So far the cost of both has been calculated theoretically [1]. We studied 50 patients using a closed system and determined the cost of administering desflurane compared with isoflurane.

Fifty unpremedicated healthy patients (aged 9–78 yr) scheduled for minor orthopaedic procedures in the day-surgery unit were allocated randomly to one of two groups. All patients were induced with propofol 2.5 mg kg^{-1} and fentanyl 1.5 μg kg^{-1} followed by introduction of laryngeal mask airway. Patients in group I received oxygen 500 ml min^{-1}, nitrous oxide 1000 ml min^{-1} and desflurane up to 12% and group II received isoflurane up to 5%, thus delivering up to 180 ml of desflurane vapour/min or up to 75 ml of isoflurane vapour/min, respectively. Breathing was assisted initially to maintain the end-tidal carbon dioxide between 5% and 6%. The fresh gas flows and the vaporizer settings were recorded at 1-min intervals throughout the procedure.

The main findings are shown in figure 6. The calculation is based on the current cost of isoflurane (£0.48/ml) and desflurane (£0.18/ml). The cost of desflurane and isoflurane is essentially the same if used in the manner described above.

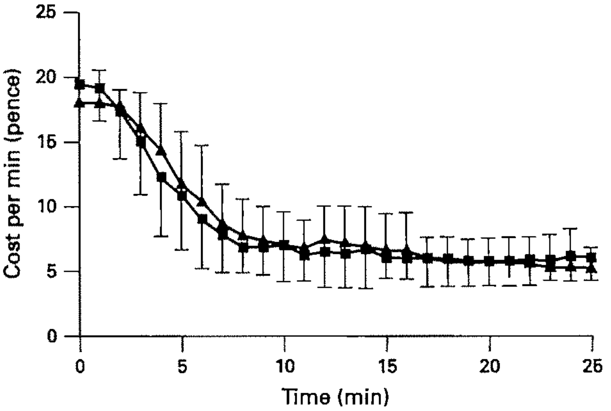


Figure 6 Comparison of costs. (▲) Desflurane; (■) isoflurane.

Induction of inhalation anaesthesia through breathing systems using carbon dioxide absorber can be achieved with fresh gas flows of 1500 ml thus further reducing the cost of anaesthetics. The cost of administering inhalation anaesthetics can be calculated by using simple arithmetic without going into complicated formulae [1–3]. It appeared that there was no significant difference between the cost of desflurane and isoflurane anaesthetic although 1 ml of isoflurane liquid was 2.6 times more expensive than 1 ml of liquid desflurane.

These findings can be explained by consideration of the relative uptake of the two agents.

Key words

Anaesthetics volatile, desflurane. Anaesthesia, audit.

References

1. Hendrickx J, De Wolf AM. *Anesthesiology* 1994; **80**: 240–242.
2. Weiskopf RB, Eger EI II. *Anesthesiology* 1993; **79**: 1413–1418.
3. Lin CY, Mostert JW, Benson DW. *Acta Anaesthesiologia Scandinavica* 1980; **24**: 354–361.

Performance of vaporizers in circle systems (II)

B. ROYSTON, G. MARKEY* AND D. WHITE
Academic Department of Anaesthesia, Northwick Park Hospital, Harrow, Middlesex

In a previous communication [1] we showed that when an in-circle vaporizer (VIC) was used with a spontaneously breathing patient a degree of self-regulation of the inspired anaesthetic concentration occurred. The patient imposed a limit on the amount of anaesthetic received and this was related to the intensity of surgical stimulus. Believing this to be beneficial we have investigated the mechanism of this effect.

The increase in inspired anaesthetic concentration with increased pulmonary ventilation could be attributed to the flow characteristics of the vaporizer—increased gas flow causing higher concentration in the output of the vaporizer. Alternatively, increased recirculation of gas through the vaporizer could be responsible.

We studied isoflurane output from the Goldman, Oxford Miniature (OMV) and Komisaroff vaporizers. A gas mixture of 33% oxygen and 66% nitrous oxide was passed through the vaporizers at a series of known flow rates between 1 and

8 litre min^{-1}. The isoflurane output concentration was measured using a calibrated Datex Capnomac Ultima. The output of the OMV showed little flow dependence whereas the Goldman and the closely similar Komisaroff vaporizers showed considerable variation with flow (fig. 7A).

Steady-state flow measurement of this type do not represent performance under clinical conditions because of the fluctuating nature of respiratory gas flow. We therefore simulated respiration using a Manley ventilator to drive gas through the vaporizer. The output of the ventilator was constricted to resemble normal respiratory flow rates. We studied the isoflurane output at varying tidal volumes and the results are shown in figure 7B. We found that with intermittent gas flow resembling normal breathing the vaporizer output was not affected by tidal volume. Peak flow and respiratory rates were also varied and found not to affect the output of the vaporizer.

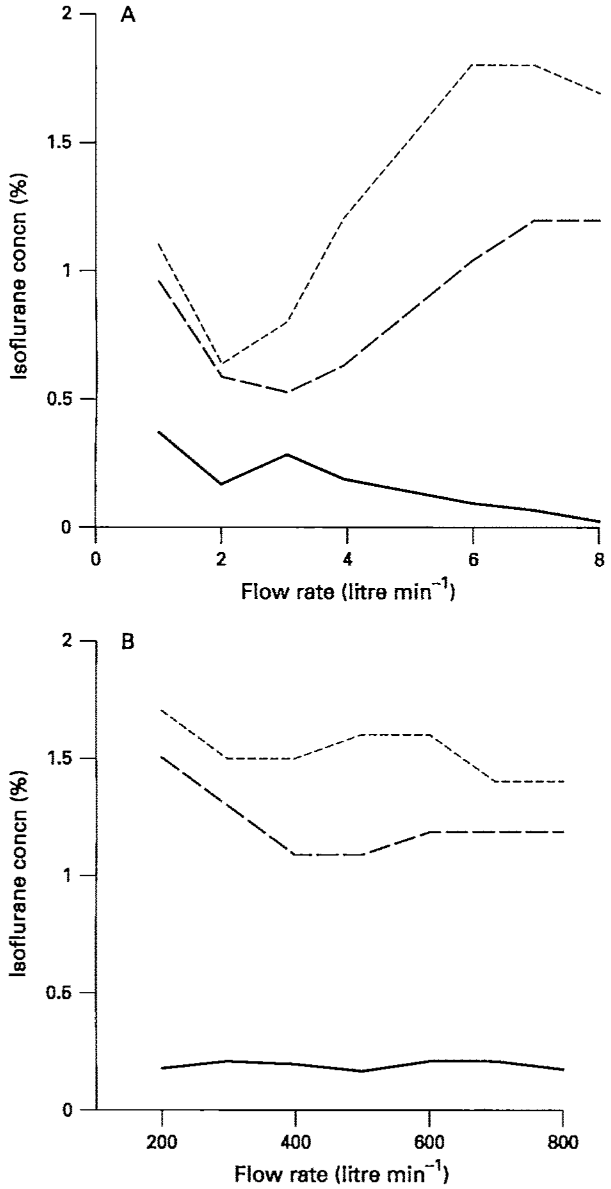


Figure 7 Results. (—) Setting 1; (— — —) setting 2; (- - -) setting 3.

We concluded that the autoregulation was not due to the flow characteristics of the vaporizer but must be attributable to recirculation. We did not exclude the possibility that pressure fluctuations in the system may contribute to autoregulation by producing a form of "pumping effect" [2].

Key words

Equipment, circle systems. Equipment, vaporizer.

References

1. Worthington L, Royston B, White D. *British Journal of Anaesthesia* 1995; 74: 228P.
2. Hill D, Lowe H. *Anesthesiology* 1962; 23: 291–298.

Extradural clonidine provides adjunctive pain relief without sedation for women in labour

M. R. TREMLETT*, J. PARKINS*, D. HUGHES* AND N. REDFERN
Department of Anaesthesia, Royal Victoria Infirmary, Newcastle-upon-Tyne

The short acting α_2 agonist, clonidine, administered at low dosage, enhances pregnancy-related analgesia to visceral but not somatic stimuli in an animal model [1]. In women in labour, a single extradural bolus of 120 µg clonidine, added to 0.125 % bupivacaine, increased the duration of pain relief but caused sedation [2]. The aim of the study was to test the hypothesis that a small initial extradural bolus of clonidine and subsequent infusion could provide adjunctive analgesia without sedation.

Women in early, established, uncomplicated labour were studied. A lumbar extradural catheter was introduced at L2–3 or L3–4, and after a test dose of 3 ml 0.5 % bupivacaine, pain relief was established with 10 ml 0.125 % bupivacaine. Once pain free, informed consent was obtained, and patients were randomized to one of two groups. The control group received a bolus of 10 ml saline, followed by an infusion of 0.03 % bupivacaine at 12.5 ml/h. The treatment group, in addition, received a bolus of 25 µg clonidine followed by 1.5 µg ml^{-1} clonidine added to the bupivacaine infusion. When pain relief was inadequate, boluses of 10 ml 0.125 % bupivacaine were given on the first two requests, and 0.25 % thereafter. Infusions were continued until delivery or obstetric intervention. Sedation was assessed on a 5-point scale from awake (= 1) to awakening only when roused (= 5).

Women in whom labour had been induced for post-maturity predominated in both groups. The addition of clonidine to 0.03 % bupivacaine resulted in a longer time to first request for additional pain relief and a smaller number of additional boluses of local anaesthetic (table 3). A difference in the degree of maternal and fetal sedation was not detected. No mother became bradycardic or hypotensive.

Table 3 Results

	Bupivacaine 0.03 % ($n = 15$) Median (range)	Bupivacaine 0.03 % + clonidine ($n = 15$) Median (range)	Mann-Whitney *U* test
First request for additional pain relief/min	97 (30–295)	195 (58–450)	$P = 0.01$
Number of additional local anaesthetic boluses requested	3 (1–6)	1 (0–3)	$P = 0.0001$
Duration of infusion/min	391 (215–873)	335 (185–735)	$P = 0.26$
Maximum level of sedation seen	1 (1–5)	1 (1–3)	$P = 0.61$

This study demonstrated that clonidine by small initial bolus and subsequent infusion can provide adjunctive analgesia without sedation for women in labour.

Key words
Analgesia, obstetric. Pharmacology, clonidine.

Acknowledgement

The authors are grateful to Boehringer Ingelheim Ltd for providing the clonidine.

References

1. Iwasaki H, Collins JG, Saito Y. *Anesthesia and Analgesia* 1991; 72: 325–329.
2. O'Meara ME, Gin T. *British Journal of Anaesthesia* 1993; 71: 651–656.

Is tramadol is better than ketorolac after day-case laparoscopy?

M. A. Sabar*, A. J. Gosling and A. S. Laurence
Department of Anaesthetics, Royal Preston Hospital

Analgesia after day-case laparoscopy is still unsatisfactory [1, 2], although improved analgesia has been obtained by aggressive use of non-steroidal agents [3]. We have compared the analgesia provided by ketorolac and tramadol after laparoscopy.

Day-case gynaecological laparoscopy patients gave signed, informed consent and had the verbal rating scale (VRS) explained whereby pain was to be assessed by a number between 0 and 10. All were anaesthetized as in previous studies using a standard propofol-fentanyl-atracurium-isoflurane anaesthetic and droperidol 0.5 mg for antiemesis.

Patients were randomized to two groups by sealed envelope. The ketorolac group were additionally given ketorolac 10 mg i.v. at induction, and discharged with six 10-mg tablets of ketorolac to take home. The tramadol group were given 1 mg kg^{-1} tramadol i.v. on induction and discharged with six 50-mg tablets of tramadol to take at home.

All patients were assessed in the recovery room for pain (VRS 0–10), nausea and vomiting (0–3) and the need for analgesia before discharge home was noted. Discharge followed the routine procedure of the unit. At about midday on the first postoperative day, all patients were contacted by telephone. An assessment of pain (0–10), nausea and vomiting (0–3), activity (0–3) and tablets consumed was made by semistructured interview. This was repeated on the second day.

We present data for the first 21 completed patients in each group (table 4). Both groups were comparable for age, weight, and duration of procedure.

There was less pre-discharge analgesia needed (not significant) in the tramadol group, despite similar recovery pain scores. Pain after discharge was, however, significantly less in the tramadol group, although by day 2 tablet consumption in both groups was similar. Nausea and vomiting were similar at all times in both groups. Activity scores in both groups were also similar. The analgesia in the ketorolac group might have been improved by increased dosage but the doses chosen were the maximum currently permitted on the product licence. The tramadol dosage was chosen to provide adequate analgesia, with minimum side effects, which we felt had been achieved.

Table 4 Postoperative indices; mean values (range) $^{*}P < 0.02$ (between groups, chi-square) $^{**}P < 0.01$ (day 1 to day 2, Wilcox) $^{***}P < 0.001$ (between groups, Mann-Whitmey) ††† $P = 0.001$ (day 1 to day 2, Wilcox)

	Ketorolac ($n = 21$)	Tramadol ($n = 21$)
Rec VRS (0–10)	2.9 (0–7)	2.7 (0–6)
Analg pre disch (Y/N)	11/21*	4/21
Day 1 VRS (0–10)	4.1 (1–8)*	2.9 (1–5)**
Day 2 VRS (0–10)	3.1 (0–6)***	2.0 (0–6)**
Day 1 activity (0–3)	1.4 (1–2)†††	1.3 (1–2)†††
Day 2 activity (0–3)	2.2 (1–3)†††	2.1 (1–3)†††
Total tablets (0–6)	3.7 (0–6)	3.8 (0–6)

Key words
Analgesics non-opioid, ketorolac. Analgesics non-opioid, tramadol. Surgery.

Acknowledgement

We thank Dr Duncan who facilitated funding for the research fellowships from NHS sources.

References

1. Smith SO, Lowrie R, Monsell F, Laurence AS. *British Journal of Anaesthesia* 1991; 67: 644–645P.
2. Teale KFH, Stickle B, Laurence AS. *British Journal of Anaesthesia* 1994; 73: 270P.
3. Ratcliffe F, Lawson R, Millar J. *Health Trends* 1994; 26: 47–49.

Changes in pineal and pituitary hormone secretion under general anaesthesia

A. Reber, P. R. Huber, W. Ummenhofer, C. Gürtler, C. Zurschmiede, Z. Khan and M. Schneider
Department of Anaesthesia and Hormone Laboratory, University of Basel/Kantonsspital, Basel and Academic Department of Anaesthesia, King's College Hospital, London

It is known that there is an association between sleep disorders and plasma melatonin concentrations [1]. There is evidence that there is a relationship between pineal and pituitary hormone secretion [2]. The secretion of the pineal hormone melatonin is stimulated by darkness and partially suppressed by benzodiazepines [3]. The effect of inhalation anaesthetics and propofol on melatonin secretion has not been reported. We investigated the influence of general anaesthesia and surgery on plasma levels of melatonin and prolactin.

Thirty-two female patients (ASA I or II) scheduled for elective gynaecological surgery (60–90-min duration) were randomized to one of two groups. Premedication consisted of 3.0 mg bromazepam orally at 07.00. General anaesthesia was performed at 08.00 with either isoflurane-nitrous oxide-oxygen-fentanyl or propofol-nitrous oxide-oxygen-fentanyl. During general anaesthesia the patients' eyes were covered allowing no light penetration. Blood samples were taken before and after premedication, immediately before induction of anaesthesia, every 15 min during anaesthesia, and hourly in the recovery room for 8 h. The control group consisted of six healthy women who underwent a similar environment and light conditions as the study groups. Blood samples were analysed for melatonin and prolactin by commercial radioimmunoassay tests. The groups were compared using non-parametric tests (a P value < 0.05 was considered as significant).

In the isoflurane group, plasma melatonin concentrations gradually increased to a peak and then decreased during the time of general anaesthesia, as they did in the control group. During propofol anaesthesia, plasma melatonin concentrations remained elevated throughout general anaesthesia. In the isoflurane group, during the recovery period the mean plasma melatonin concentration was higher than that obtained in the propofol and control groups, between which there was no difference. Prolactin significantly increased after induction of anaesthesia and decreased postoperatively to the baseline (before premedication) in the isoflurane and propofol groups. In the control group there was no change in plasma prolactin concentrations.

Isoflurane and propofol anaesthesia as well as darkness led to elevated plasma melatonin concentrations which continued in the recovery period in contrast with prolactin. An increase in plasma melatonin during darkness did not lead to an increase in plasma prolactin concentrations. This evidence disputed the relationship between melatonin and prolactin release. The increased concentrations of melatonin may affect recovery from anaesthesia.

Key words
Anaesthesia, general. Hormones, melatonin.

References

1. Dahlitz M, Alvarez B, Vignau J. *Lancet* 1991; 337: 1121–1124.
2. Johnston E, Ferrier I. *British Journal of Clinical Pharmacology* 1980; 10: 5–21.
3. McIntyre IM, Norman TR, Burrows GD. *Chronobiology International* 1993; 10: 205–213.

Patient-controlled analgesia and the plasma glucose response to surgery

V. O'Keefe, M. M. van Miert, C. J. R. Parker, P. Salmon and A. Shenkin
Departments of Anaesthesia, Clinical Psychology and Clinical Chemistry, University of Liverpool

Perioperative analgesia has a limited effect on the metabolic response to surgery [1]. Being able to control a stressful event may diminish its physiological effects [2]. Patient-controlled analgesia (PCA) requires the patients to assume control of part of their own treatment; we, therefore, decided to study the effect of PCA on the physiological response to a given surgical insult.

Thirty-three patients about to undergo mastectomy were studied. After written informed consent, they completed baseline questionnaires to assess trait and state anxiety (Spielberger inventories), and health-specific locus of control beliefs [3]. The latter has four subscales related to beliefs about the effect on health of self control, health care providers, chance and general threats. The patients were then randomized to receive either patient-controlled i.v., or conventional i.m. analgesia. Surgery was scheduled to start between 08.30 and 11.30. Premedication was with diazepam 10 mg orally, 2 h preoperatively. Anaesthesia was induced with morphine 0.1 mg kg^{-1}, up to a maximum of 10 mg, and thiopentone 150–425 mg, followed by atracurium, and maintained with oxygen, nitrous oxide and isoflurane. Venous blood samples were taken for plasma glucose estimation before induction of anaesthesia, and at 2, 4, 6, 8, 10, 12 and 24 h after skin incision. Postoperative analgesia was provided either with morphine 10 mg i.m., given by the nursing staff, on request from the patient, or by morphine from a patient-controlled analgesia device programmed to deliver a 1-mg bolus, with a 5-min lockout period and no background infusion. Prochlorperazine 12.5 mg i.m. was given if required. Pain was assessed with a visual analogue scale (0–10) at 4, 8, 12 and 24 h after incision. On the day after surgery the patient completed the Spielberger state anxiety inventory and other questionnaires to assess their perception of control over their pain relief. The area under the curve of plasma glucose vs time from 0–12 h after the incision was calculated. Differences between the groups were assessed using the *t* test, and the effect of other factors on the glucose response using univariate and multivariate regression.

Although the mean morphine dose was more than twice as great in the PCA group as in the i.m. group, average pain scores were not significantly different (table 5). There was a significant difference between the groups in the area under the curve of plasma glucose up to 12 h ($P < 0.05$). In multivariate regression, the plasma glucose response was also significantly greater in subjects with high trait anxiety ($P < 0.05$). There was no significant correlation between glucose response and either operation type, average pain score, morphine dose, preoperative state anxiety or any subscale of the locus of control inventory.

Patient-controlled analgesia reduced the glucose response in the first 12 h after mastectomy. The plasma glucose response was also significantly greater in subjects with high trait anxiety.

Key words
Analgesia, patient-controlled. Blood, glucose.

Table 5 Results (mean (SD)) (I.m. = intramuscular analgesia, PCA = patient-controlled analgesia)

	I.m. ($n = 16$)	PCA ($n = 17$)	
Age (yr)	61.2 (9.9)	53.9 (12.8)	
Operation (simple/modified radical)	7:9	10:7	
Trait anxiety	39.2 (8.7)	39.2 (5.4)	
Postoperative morphine dose in first 24 h (mg)	10.2 (9.4)	24.6 (19.8)	$P < 0.05$
Average pain score 4–12 h postoperatively	2.4 (1.7)	2.0 (1.4)	n.s.
Glucose AUC 0–12 h (mmol h $litre^{-1}$)	81.1 (12.2)	71.0 (11.6)	$P < 0.05$

Acknowledgement

This study was supported in part by a grant from Abbott plc.

References

1. Editorial. Analgesia and the metabolic response to surgery. *Lancet* 1985; i: 1018–1019.
2. Lundberg U, Frankenhauser M. *Biological Psychology* 1978; 6: 51–59.
3. Lau RR, Ware JF. *Medical Care* 1981; **19**: 1147–1158.

Flow cytometry evaluation of the *in vitro* effects of four i.v. anaesthetics on the respiratory burst of human neutrophils

M. Leuwer, J. F. Heine, L. Arseniev, D. Scheinichen, K. Jäger and S. Piepenbrock
Departments of Anaesthesiology and Haematology, Hannover Medical School, Germany

The production of oxygen radicals (respiratory burst) is one of the most important functions of neutrophil granulocytes [1]. Alteration of this defence mechanism by drugs may favour bacterial infections. Because it has not yet been shown that anaesthetic agents inhibit some other aspects of neutrophil function [2], we investigated the influence of propofol, thiopentone, methohexitone and midazolam on the respiratory burst (RB) of neutrophils *in vitro* via flow cytometry.

After the local Ethics Committee's approval venous blood was drawn from 20 healthy donors. Leucocytes were obtained as supernatant after sedimentation (1 g). The sedating, anaesthetic, 10-fold sedating and 10-fold anaesthetic plasma concentration effects of the four investigated agents on the RB were measured by means of the intracellular oxydation of dihydrorhodamine-123 to the fluorescent rhodamine-123 [3]. All results were expressed as a percentage of inhibition of the positive control response, which was the RB after maximum stimulation by phorbol myristate acetate (PMA) in the absence of anaesthetic agents. Prestimulation of neutrophils was quantified by negative controls (RB without stimulation by PMA in the absence of anaesthetic agents). Viability discrimination was performed by addition of propidium iodide just before measurement. Data were stored in listmode data files using FACScan software and analysed with PC-LYSYS software on a personal computer. Results are expressed as mean values and standard deviations. They were evaluated statistically using Wilcoxon or Mann-Whitney *U* test. $P < 0.05$ was considered to be significant.

At anaesthetic plasma concentrations propofol caused a significant ($P < 0.01$) higher depression of the RB (7.3 (SD 6.0)%) than thiopentone (4.5 (5.3)%), methohexitone (0.9 (1.6)%) and midazolam (2.2 (2.7)%) respectively. At sedating plasma concentrations propofol produced 3.5 (5.6)% inhibition. Methohexitone (1.3 (2.1)%) and midazolam (1.3 (1.7)%) showed minimum effects. At 10-fold anaesthetic concentrations the RB inhibition by propofol was almost complete (90.8 (3.9)%). At the given plasma concentrations the inhibitory effects of its solvent 10% Intralipid alone were nearly identical to those of propofol.

Propofol produced markedly more RB inhibition than thiopentone, methohexitone and midazolam at all plasma concentrations investigated. Its suppressive effects may be due to its lipid carrier 10% Intralipid. It may be worthwhile, therefore, to investigate the effects of other lipid solutions on the RB of neutrophils.

Key words
Anaesthetics, i.v. Blood, neutrophils.

References

1. Babior BM. *New England Journal of Medicine* 1989; **298**: 712–725.
2. O'Donnell NG, McSharry CP, Wilkinson PC, Asbury A. *British Journal of Anaesthesia* 1992; **69**: 70–74.
3. Rothe G, Oser A, Valet G. *Naturwissenschaften* 1988; **75**: 354–355.

Pulmonary lactate flux after cardiopulmonary bypass

V. Kulkarni, H. McFarlane and N. R. Webster
University Department of Anaesthesia and Intensive Care, Aberdeen Royal Infirmary, Aberdeen

Postperfusion pulmonary dysfunction syndrome after cardiopulmonary bypass (CPB) is characterized by an increase in interstitial fluid, sequestration of neutrophils and increased pulmonary shunting. Though the injury commonly resolves after the operation, it can occasionally progress to adult respiratory distress syndrome (ARDS). The aetiology is manifold. Microaggregates in the pulmonary circulation and release of vasoactive mediators from platelets have been demonstrated [1]. A systemic inflammatory response to CPB with increasing concentrations of tumour necrosis factor-α (TNFα), IL-8 and C3 is accompanied by C3-mediated expression of CD18 and subsequent neutrophil sequestration [2]. During CPB there is no pulmonary circulation and bronchial blood flow is low. The pulmonary tissues are only reperfused after the return of normal circulation leading to ischaemia/reperfusion injury. Ischaemic tissues commonly produce lactate. Significant lactate production by the lung has been shown recently to occur in cases of lung injury from sepsis and ARDS [3]. Though it is known that whole body lactate concentrations increase after CPB there has been no study of pulmonary lactate production. The present study was designed to determine whether there is significant lactate production by the lung, following pulmonary ischaemia/reperfusion injury, after CPB.

Six patients aged 45–64 yr undergoing elective coronary artery bypass surgery were included in the study after Ethics Committee approval. Before commencement of CPB a 5-ml sample of blood was collected in a heparinized tube, simultaneously from the indwelling arterial and pulmonary artery catheters and stored in ice. Cardiac output and blood gases were also measured. Blood flow during bypass was maintained at 2.4 litre m^{-2} min^{-1}. After CPB, on resumption of normal circulation, the measurement sequence was repeated. Blood samples were centrifuged and the plasma stored at −20 °C before assay. Lactate measurements were made using the Analox PGM-7 analyser (Analox Instruments, London).

Normally there is either a slight decrease (negative flux), or no change in lactate across the lung. After bypass lactate concentrations were higher. Though the prebypass situation of a negative or zero flux was seen in most of the cases, two patients showed the lung producing significant quantities of lactate, calculated to be 190.8 mmol and 124.8 mmol every h. There was no relationship with the duration of bypass, the number of grafts or complications during operation. Both patients did, however, have documented preoperative pulmonary disease and needed prolonged postoperative management.

Table 6 Arterial (A) and mixed venous (MV) lactate concentrations (mmol $litre^{-1}$) before and after cardiopulmonary bypass

	Before bypass			After bypass		
No.	A	MV	Flux	A	MV	Flux
1	1.5	1.5	0	2.5	2.5	0
2	1.7	1.8	−0.1	3.7	4.0	−0.3
3	1.8	1.8	0	2.7	2.6	+0.1
4	1.7	1.6	+0.1	2.9	3.1	−0.2
5	1.6	1.7	−0.1	3.8	3.2	+0.6
6	1.4	1.5	−0.1	3.0	2.6	+0.4

Key words
Surgery, cardiovascular. Lung, pathophysiology. Metabolism, lactate.

References

1. Zehr KJ, Poston RS, Lee PC. *Annals of Thoracic Surgery* 1995; 59 (2): 328–335.
2. Gillinov AM, Redmond JM, Winkelstein JA. *Annals of Thoracic Surgery* 1994; 57 (2): 345–352.
3. Bellomo R, Kellum J, Kramer D, Pinsky M. *Anaesthesia and Intensive Care* 1995; 23: 379.

Org 21465 a new i.v. anaesthetic agent

C. J. Daniell, M. Cross, J. R. Sneyd, P. Thompson,
M. M. Weideman* and C. J. Andrews
Department of Anaesthesia, Derriford Hospital, Plymouth, Phase I Clinical Trials Unit, Plymouth and Organon Teknika NV, Turnhout, Belgium

Org 21465 is a water-soluble steroidal i.v. anaesthetic. *In vitro* studies have shown that Org 21465 has a higher degree of selectivity for the GABA-A receptor than thiopentone or propofol. *In vivo* studies in rodents, dogs, pigs and primates have demonstrated favourable hypnotic properties.

Ten healthy male volunteers aged 22–28 yr weighing 63–98 kg each received a single dose of Org 21465, 0.8–1.8 mg kg^{-1} by infusion over 1 min. An infusion of the solvent vehicle of identical volume preceded each active infusion by 15 min.

After arterial and venous cannulae had been placed in opposite arms, subjects rested quietly and received supplementary oxygen by a nasal cannula. Direct arterial pressure, oxygen saturation, ECG, bio-impedance cardiac output, and EEG were monitored continuously. Arterial samples were obtained for pharmacokinetic analysis. Subjects held a 20-ml water-filled syringe in one hand.

Table 7 Clinical responses to Org 21465. Times (min) from the start of drug infusion (means) and individual values

	Dose (mg kg^{-1})				
	0.8	1.0	1.2	1.5	1.8
No.	1	2	3	2	2
Loss of verbal contact	2.5	(1.00) 1.17, 0.83	(1.11) 1.45, 1.00, 0.87	(0.91) 0.83, 0.98	(0.59) 0.42, 0.77
Drop syringe	N/A	(1.17) 1.35, 0.98	(1.01) 1.17, 1.25, 0.78	(0.97) 0.95, 0.98	(0.78) 0.78, 0.77
Loss of eyelash reflex	N/A	(2.98) 3.17, 2.80	(2.19) 2.50, 1.50, 2.58	(1.45) 1.33, 1.57	(2.27) 0.87, 3.66
Eyes open on command	N/A	(9.96) 5.87, 14.05	(11.72) 17.25, 8.78, 9.12	(15.92) 15.50, 16.33	(19.25) 17.5, 21.00
Move limbs on command	N/A	(9.87) 6.23, 13.5	(13.17) 18.00, 10.50, 11.00	(18.14) 16.35, 19.93	(20.00) 19.00, 21.00

All subjects complained of discomfort during injection of the solvent and during injection of Org 21465. The subject who received 0.8 mg kg^{-1} stopped speaking at 150 s but did not lose his eyelash reflex or drop the syringe. Subjects receiving 1.0 mg kg^{-1} or more, became anaesthetized (table 7).

There was no evidence of histamine release and apnoea did not occur, even at the highest dose. Cardiovascular stability was seen in all subjects. Excitatory phenomena were observed in seven subjects and were dose related, no spikes were seen on the EEG. One subject coughed repeatedly after receiving 1.8 mg kg^{-1} of Org 21465, another had episodes of sneezing after the same dose. Hypoxaemia did not occur in any subject.

A dose of 1.0 mg kg^{-1} of Org 21465 induced a short period of anaesthesia followed by a slow recovery. Higher doses caused excitation.

Key words
Anaesthetics, i.v. Recovery.

Acknowledgement

Supported by Organon Teknika.

Effects of dopamine and dopexamine on splanchnic microcirculation during major surgery in humans

M. C. Bellamy, Y. Young, P. J. Guillou* and H. O'Beirne
Departments of Anaesthesia and Surgery, St James's University Hospital, Leeds

Most studies on splanchnic microcirculation have used microsphere techniques in animals. Relatively little is known of the factors governing intraoperative splanchnic blood flow in humans. We have, therefore, studied the effects of dopexamine and dopamine on small bowel and hepatic microcirculatory flow during major surgery in humans by a non-invasive technique (laser Doppler flowmetry).

Ethics Committee approval was obtained for this prospective randomized single-blind crossover study. Ten adult patients undergoing major upper abdominal surgery gave informed consent. After premedication with temazepam 20 mg, anaesthesia was induced with thiopentone 3 mg kg^{-1} and fentanyl 3 μg kg^{-1}. Neuromuscular block was facilitated by infusion of atracurium. The lungs were ventilated with isoflurane (1 MAC) in oxygen-enriched air. Patients were allocated randomly to receive dopexamine 1 μg kg^{-1} min^{-1} or dopamine 3 μg kg^{-1} min^{-1} by continuous i.v. infusion. After abdominal incision, steady-state jejunal (GBF) and liver blood flow (LBF) in segment III were assessed by laser Doppler flowmetry. The measurements were repeated after 30 min infusion of inotrope. The inotrope was then swapped and measurements repeated after a further 30 min. Data were analysed using paired Student's *t*-test and multiple regression analysis.

There were no differences in haemodynamics between periods of dopamine and dopexamine administration.

Multiple regression described liver blood flow as (CVP × 7.4) − (50 if dopamine rather than dopexamine) + 65, $P < 0.01$, $r^2 = 0.51$.

We have shown that during major surgery under isoflurane anaesthesia in humans, dopexamine produced higher liver microcirculatory blood flow than did dopamine. In this model, 51 % of the variability in liver blood flow was accounted for by the use of dopexamine rather than dopamine, and volume loading. However, dopexamine conveyed no improvement in gut blood flow over dopamine, nor were there any differences in haemodynamics between administrations of the two drugs (table 8). These results were consistent with local effects on hepatic arterial flow mediating the observed changes. These results may have important implications for anaesthesia of the high-risk surgical patient.

Table 8 Results

	Flow/PU Mean (SEM)	*P* value
Gut		
dopamine	170 (37)	0.81
dopexamine	160 (41)	
Liver		
dopamine	76 (38)	< 0.05
dopexamine	115 (54)	

Key words
Liver. Blood flow. Sympathetic nervous system, dopexamine.

Predictability of tumour necrosis factor concentration: evidence for a mechanism for mutual regulation of autacoids in systemic inflammatory response syndrome

Alison J. Pittard, N. R. Webster and M. C. Bellamy
Intensive Care Unit, St James's University Hospital, Leeds and Department of Anaesthesia and Intensive Care, Aberdeen Royal Infirmary, Aberdeen

Uncontrolled release of cytokines and adhesion molecules is thought to be of major importance in the systemic inflammatory response syndrome (SIRS) and severe sepsis (SS) [1]. We have therefore studied inter-relationship of autacoids in SIRS and their effect on outcome.

Fifty-five consecutive patients presenting to intensive care with SIRS or SS were studied. A volume of 10 ml of blood were collected into a heparinized tube within 12 h of admission, centrifuged, aliquoted and frozen at −20 °C until analysis. ELISA was used to measure the following autacoids: soluble E selectin (sE-selectin), soluble P selectin (sP-selectin), soluble E cadherin (sE-cadherin), soluble tumour necrosis factor receptor type two (sTNF RII), tumour necrosis factor alpha (TNFα), interleukin-1 receptor antagonist (IL-1ra) and the interleukins 1b, 6, 8 and 10 (IL-1b, 6, 8, 10). Outcome was measured as survival until intensive care discharge. Data were fitted to a logistic regression model (for survival) or multiple linear regression (for cytokine inter-relationships) model using backward stepwise selection.

Forty-four patients died (80 %) and 11 survived (20 %). We were unable to identify a cytokine/adhesion molecule pattern predictive of survival. However, using TNFα as the dependent variable, a regression equation was derived which predicted TNFα levels from those of other autacoids: TNFα = 52.29 + 1.88 (sE-cadherin) − 0.07 (sE-selectin) + 0.21 (IL-10) − 0.09 (IL-1b) − 8.77×10^{-4} (IL-1ra) + 0.01 (IL-6) − 0.04 (sP-selectin) − 8.72×10^{-4} (sTNF-RII). $P < 0.00001$, $F = 7.0 \times 10^{15}$ and $r^2 = 1$.

This equation applied irrespective of patient outcome. It allowed accurate prediction of any autacoid given concentrations of other autacoids. These findings challenge the orthodox view that in SIRS, cytokine and inflammatory mediator release is excessive and uncontrolled [2, 3].

Key words
Protein, Autacoids. Complications, systemic inflammatory response syndrome.

Acknowledgements

We wish to acknowledge the gift of ELISA kits from R&D systems, Oxford and financial support from the Intensive Care Society.

References

1. Bone RC. *Chest* 1992; **101**: 1644–1655.
2. Glauser MP, Zanetti G, Baumgartner JD, Cohen J. *Lancet* 1991; **338**: 732–736.
3. Goris JA, TE Boekhorst TPA, Nuytinck JKS. *Archives of Surgery* 1985; **120 (10)**: 1109–1115.

White blood cell cytosolic calcium changes during human orthotopic liver transplantation

S. Enright* and M. C. Bellamy
Departments of Anaesthesia and Intensive Care, St James's University Hospital, Leeds

Reperfusion syndromes are frequently associated with increases in cytosolic calcium. The haemodynamic and biochemical effects of the reperfusion syndrome during human orthotopic liver transplantation (OLT) have been characterized [1–3]. Arachidonic acid

Table 9 Results (interquartile range). *Not significant, $P = 0.46$; **adjusted P value = 0.0008

	Baseline	Before reperfusion	After reperfusion
Intracellular calcium (nmol litre^{-1}) $P = 0.0002$	10.8 (6.4–23.1)*	16.7 (8.2–27)**	24.9 (16.2–50)**
Calcium influx (nmol litre^{-1} s^{-1}) $P = 0.009$		7.4 (4.6–13.5)	8.9 (5.7–33.3)

metabolites mediate increases in intracellular calcium, and thus potentiate the effect of free radicals. This study was carried out to characterize white blood cell (WBC) calcium changes as a mediator for white cell activation in human OLT.

Ethics Committee approval was obtained. Twenty consecutive patients scheduled for OLT gave informed consent. All patients were anaesthetized according to our standard technique [1]. Blood samples were drawn into lithium heparin tubes for estimation of WBC cytosolic calcium at induction of anaesthesia, 5 min before graft reperfusion, and 15 min after reperfusion. WBC were immediately separated using sucrose slope centrifugation, and intracellular calcium assayed using the FURA 2AM technique. Additionally, the rate of increase in intracellular calcium after addition of 1 mmol solution of calcium chloride to the extracellular milieu was used as an estimate of membrane calcium permeability. Induction, before and after reperfusion cytosolic calciums were compared using Friedman's two-way analysis of variance by rank for non-parametric data. Specific differences were assessed using Bonferroni-corrected Wilcoxon signed rank test for paired data. Pre- and post-reperfusion WBC membrane permeabilities were compared using Wilcoxon signed-rank test.

Results were expressed as median (interquartile range) (table 9).

We demonstrated a significant increase in WBC membrane permeability for calcium and cytosolic calcium concentration following reperfusion in human OLT. These results were consistent with WBC activation at reperfusion [2].

Key words
Ions, calcium. Complications, reperfusion syndrome.

References

1. Webster NR, Bellamy MC, Sadek SA, Lodge JPA. *British Journal of Anaesthesia* 1994; 72 (4): 418–421.
2. Bellamy MC, Goode HF, Webster NR. *British Journal of Anaesthesia* 1994; 73 (5): 717–718.
3. Webster NR, Bellamy MC, Goode HF. *Anesthesiology* 1994; 81 (3a): A164.

Immunoglobulin and interleukin 2 production *ex vivo/in vitro* during treatment with oral retarded morphine

S. Palm, S. Letzen, J. Steinmann and C. Maier
Clinic of Anesthesiology and Operative Intensive Care,
Department of Immunology, Christian-Albrechts-University, Kiel,
Germany

Clinical indications for the use of morphine have, nowadays, been extended towards non-malignant pain syndromes. Suspected inhibitory effects of morphine on immune functions, mostly described in animal experiments and in drug addicts, have thus to be investigated in clinical settings [1].

Ten patients (age 31–65 yr; eight non-malignant, two malignant pain syndromes) and healthy controls ($n = 9$) were investigated. Blood samples were drawn before (basal status), after 1 and 4 weeks of treatment with oral retarded morphine 30–240 mg day^{-1}. Peripheral mononuclear cells were cultured with/without concanavalin A (5 μg ml^{-1}) for interleukin-2 (pg ml^{-1}; IL2) production (24 h), pokeweed mitogen (PWM; 1 μg ml^{-1}) for immunoglobulin G/M (IgG/M) production (7 days). Variables were measured by ELISA. Statistics were performed using the Wilcoxon matched pairs and Mann-Whitney U test ($P < 0.05$).

Patients produced less IgG/M in comparison with controls at basal status. PWM stimulation of Ig production was reduced for IgM after 1 and 4 weeks of morphine treatment, whereas concentration ranges in controls remained unchanged, IL2 tended towards increased values during morphine treatment.

Table 10 Immunological variables in patients with chronic pain syndromes during treatment with oral retarded morphine (Depicted are medians, below 25th/75th percentile, * lower *vs* control († $P < 0.05$, ‡ $P < 0.1$), ** elevated *vs* basal status, (+) significantly stimulated over 0 μg ml^{-1} PWM ($P < 0.05$))

	Basal status		Morphine treatment (weeks) 1		4	4–12
	Patient	Control	Patient	Control	Patient	Control
IgM plasma concentration (g/l):						
	0.9	1.3	0.9	1.4	1.4	1.5
	0.7/1.9	0.6/2	0.8/2.1	0.5/1.7	0.8/1.6	0.8/1.8
PWM (0 and 1 μg/ml) stimulated cell culture (ng/ml):						
0	210*	281	240	303	187	113
	80/310	210/680	80/480	150/1200	110/610	60/350
1	1075 (‡, +)	1203 (+)	483 (+)	2484 (+)	377	1583
	80/1510	470/2810	200/1830	860/6670	190/500	420/2030
IgG plasma concentration (g/l):						
	12.4	14.6	13.1	14.7	13.1	16.6
	11.3/15.0	9.3/16.3	9.9/17.2	10.5/17.0	11.6/13.6	14.2/17.6
PWM (0 and 1 μg/ml) stimulated cell culture (ng/ml):						
0	446*	820	734**	997	868	381
	270/740	590/1160	440/1050	500/4650	420/1430	340/640
1	809* (+)	2233 (+)	927	2044 (+)	775	1631
	470/3200	920/3130	610/2600	1260/9820	610/1670	570/2390
n	10	9	10	7	7	4
IL2	146.9	95.9	256.5	136.3	693.1	257.7
	79/279	66/184	145/701	89/223	305/958	135/371
n	8	7	8	6	6	4

The results indicated that CD 19 cells of pain patients had a reduced ability to produce IgG/M after stimulation. Morphine treatment seemed to aggravate this defect. Distribution of lymphocyte subpopulations remained unchanged [2] (table 10). The clinical relevance of these results needs to be evaluated further during stimulation of immune function.

Key words
Analgesics opioid. Morphine. Immune response. Protein, immunoglobulins.

References

1. Rouveix B. *Therapie* 1992; 47: 503–512.
2. Palm S. *Der Anaesthesist* 1994; 43: S248.

Parental or anaesthetist's ability to predict a 'stormy' induction in young children

B. Lyons, F. Kirby and W. Casey
Department of Anaesthesia, Our Lady's Hospital for Sick Children, Crumlin, Dublin, Ireland

Induction of anaesthesia is a frightening event for many children, and if stormy, may result in subsequent psychological disturbance [1]. Several features have been shown to increase the likelihood of an adverse emotional reaction to anaesthesia including patient age, previous anaesthetics and parental behaviour [2]. Premedication of these children may reduce the incidence of difficult inductions, but is often omitted in day-case patients to avoid delayed discharge. It would be useful to identify those children who will suffer a stormy induction, but anaesthetists are poor at predicting this [2]. Parents, however, have witnessed their child's reaction to a variety of stressful situations and thus are more likely to predict accurately the response to induction. The aim of this study was, therefore, to compare anaesthetists' and parents' ability to predict a child's reaction to induction of anaesthesia.

Eighty-five ASA I unpremedicated children, aged 1 to 5 yr and undergoing minor day-case surgery were enrolled after parental consent. Children were seen by an anaesthetist on the day ward, who tried to predict how difficult the induction was likely to be using a three-point scale (smooth, fair, difficult/stormy). Parents were also asked to predict how well their child would cooperate with induction. All children were accompanied by one parent to the anaesthetic room. The induction technique was decided on by an uninvolved, blinded anaesthetist who scored the child's cooperation with induction using a three-point scale [2]. Data were analysed using Student's-t or chi-square tests.

The 85 children included 49 males and 36 females of whom 59 (64%) underwent a difficult induction. Children who had undergone a previous general anaesthetic were less likely to co-operate with induction ($P < 0.05$), but sex, anaesthetist's grade or induction technique were not related to behaviour. Parents predicted correctly the behaviour of 48 of the 59 children (81%) who underwent a stormy induction, and 16 of the 26 (62%) who had a smooth or fair induction. The anaesthetist predicted correctly the behaviour of 49% and 62% of difficult and smooth/fair inductions respectively ($P < 0.05$ compared with parents).

This study demonstrated the high incidence of young children who undergo a difficult anaesthetic induction. Parents were more accurate at predicting unsatisfactory behaviour than the anaesthetist. Therefore prior consultation with parents may assist in identifying children who would benefit from additional psychological or pharmacological preparation before ambulatory surgery.

Key words
Anaesthesia, paediatric. Psychological responses. Children.

References

1. Meursing A. *Current Opinions in Anaesthesiology* 1989; 2: 335–338.
2. Rosen DA, Rosen KR, Hanallah RS. *Paediatric Anaesthesia* 1993; 3: 365–370.

Midazolam *vs* trimeprazine premedication for children during day-care surgery

D. Nathwani*, P. Rich, K. M. Konieczko and V. Ramachandra
Academic Department of Anaesthesia, St Mary's Hospital Medical School, Northwick Park Hospital, Harrow

Premedication in children should reduce anxiety and facilitate induction of anaesthesia without prolonging the recovery period [1]. Midazolam has been shown to be an effective oral premedicant [2]. We compared midazolam and trimeprazine for children undergoing ear, nose and throat day-case surgery. After approval by Harrow Research Ethics Committee, and informed parental consent, 40 children [ASA I and II] aged 2–6 yr were studied. They received at random either oral midazolam 0.5 mg kg^{-1} and atropine 15 μg kg^{-1} 30 min before operation ($n = 20$) or trimeprazine 2 mg kg^{-1} and atropine 15 μg kg^{-1} 90 min before operation ($n = 20$). Induction was with thiopentone 5 mg kg^{-1} or by inhalation of halothane. Either a laryngeal mask airway or a tracheal tube was inserted (with suxamethonium 1 mg kg^{-1}). Anaesthesia was maintained using 67% nitrous oxide in oxygen and isoflurane. Postoperative analgesia was provided by diclofenac suppositories 12.5–25 mg. The rate and quality of recovery was assessed by the children inserting coloured shapes into a container through the appropriate holes in the lid, 2 and 4 h after the operation. The child had three attempts at the game and the number of shapes inserted in 45 s was recorded. Before induction an independent observer recorded anxiolytic and sedation scores and tolerance of induction. The ward nurses recorded vomiting up to 2 and 4 h. Fisher's exact test compared awake/asleep and vomiting, and the Mann-Whitney U test compared the median changes in scores.

At induction, sedation, anxiolytic and tolerance scores were not significantly different, confirming that the drugs at the doses given were equally effective. Within the 4-h recovery period none of the midazolam group vomited compared with eight of the trimeprazine group ($P = 0.003$). The psychometric testing could only be performed by awake children. At 2 h, seven trimeprazine and 18 midazolam children were awake, $P = 0.001$ (at 4, 15 and 20 h $P = 0.05$).

We found that midazolam had a faster rate and better quality of recovery from anaesthesia than trimeprazine (table 11). At 4 h none of the midazolam patients had any clinically significant impairment.

Table 11 Number of children showing a reduction (0 to 5) in psychometric scores from preoperative baseline. (T = trimeprazine and M = midazolam group)

Reduction in score from baseline	At 2 h T	At 2 h M		At 4 h T	At 4 h M	
0	0	4		1	11	
1	1	8		0	9	
2	3	5	$P = 0.001$	8	0	$P < 0.001$
3	1	1		2	0	
4	1	0		4	0	
5	1	0		0	0	

Key words
Premedication. Children. Hypnotics benzodiazepine, midazolam. Hypnotics benzodiazepine, trimeprazine. Surgery, day-case.

References

1. White PF *Anesthesia and Analgesia* 1986; 65: 963–974.
2. McMillan CO, Spahr-Schopfer JA, Sikich N, Hartley E, Lehman J. *Canadian Journal of Anesthesia* 1992; 39: 545–550.

POSTER PRESENTATIONS

Evaluation of an oesophageal intubation detector device using electrical resistance

C. D. Deakin*
Department of Anaesthetics, Queen Victoria Hospital, East Grinstead, West Sussex

Difficult intubation is a common problem with maxillofacial and burns patients. As many as 30% of all deaths attributable to anaesthesia are due to failure to manage difficult airways, particularly unrecognized oesophageal intubation [1]. Several methods of confirming correct tracheal tube (TT) placement have been described [2] but none gives an immediate indication of successful intubation.

An electrical circuit was constructed to measure the resistance of the tissues between the skin overlying the cricothyroid membrane and the tip of the tracheal tube. A small self-adhesive foil patch (1 × 1 cm) was placed on the anterior surface of the cuff of an appropriately sized TT. Soft dental wire was attached behind the foil and run up the body of the tracheal tube. The TT body and wire were wrapped in polytetrafluoroethylene (PTFE) tape. An electrical meter measuring resistance was then attached to the dental wire and the circuit completed by connection to a disposable skin electrode placed over the cricothyroid membrane. The electrical resistance of the dental wire and foil patch alone was $< 0.01\ \Omega$.

Ten patients undergoing routine surgery requiring intubation were studied. After induction of anaesthesia and paralysis with vecuronium, the TT was placed first in the trachea under direct vision and the cuff inflated until any air leak ceased. Correct TT placement was confirmed by capnography. Resistance was measured. The cuff was then deflated and the oesophagus intubated under direct vision. The cuff was reinflated with the same volume of air used when placed in the trachea. A measurement of resistance was taken again. The experimental TT was then withdrawn and a standard TT inserted for the remainder of anaesthesia.

All results are expressed as mean (1 SD). Analysis of electrical resistance was by a single-tailed paired t test.

Five male and five female patients were studied, age 38.9 (16.0), body mass index 25.1 (5.1), neck circumference 36.2 (2.4) cm. The resistance when the TT was placed in the trachea was 65.1 (43.6) kΩ. The resistance when the TT was placed in the oesophagus was 1350.0 kΩ (503.9) $P = 0.0001$ (fig. 8).

There were no complications with this technique.

Measurement of electrical resistance across the tissues of the neck is a new method of detecting correct TT placement. Unlike other techniques, electrical resistance provides an instantaneous indication of tracheal or oesophageal intubation. This technique may have an application in the management of difficult intubation.

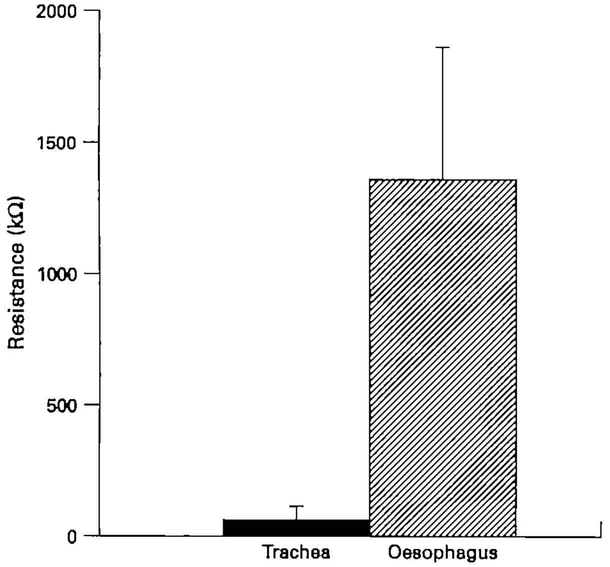


Figure 8 Mean resistance (1 SD) measured from the trachea and oesophagus.

Key words
Intubation, tracheal. Airway.

References

1. Benumof JL. *Anesthesiology* 1991; 75: 1087–1110.
2. Fell D. In: Nimmo W, Rowbotham DJ, Smith G, eds. *Anaesthesia*. Oxford: Blackwell Scientific Publications, 1994: 523–524.

Haemodynamic effects of air travel

I. Malagon
Intensive Care Unit, St James Wing, St George's Hospital, London

Cardiovascular events are the leading cause of death during commercial air travel. It is well known that arterial pressure suffers minimal changes at moderate altitude [1, 2]. Heart rate begins to increase at 4000 ft as a response to hypoxia [3]. This pilot study assesses the changes in cardiac output and stroke volume during air ambulance repatriation. The results show that exposure to moderate altitude during air ambulance transport induces changes in stroke volume not described before.

Five medical crew members and three patients with a median age of 30 (range 26–74) yr agreed to participate in the study. The subjects were transported by commercial air ambulance. Heart rate, ECG, oxygen saturation and arterial pressure were measured. There were no changes in respiratory rate, the ambient temperature inside the cabin remained between 18 and 21 °C, and two of the subjects had oxygen therapy. None underwent ventilation of the lungs.

Cardiac output was measured with suprasternal Doppler. Stroke distance (SD) is the length a column of blood travels along the aorta with each ventricular stroke, and it is equivalent to stroke volume. Minute distance (MD) is the product of stroke distance and heart rate. For the ascending aorta this is a linear index of cardiac output. Each reading is an average of three measurements.

Each patient had a reading taken before take off, 5 min after take off, 5 min after reaching cruising altitude (between 5000 and 8000 ft inside cabin pressure), and 5 min after descent was initiated. Statistical analysis of the results was performed using ANOVA with Scheffe correction. Between-group statistical significance of $P < 0.05$ is individually stated. The results are presented in table 12.

Key words
Air ambulance. Heart, cardiac output.

References

1. Savonitto S, Cardellino G, Sardina M. *Cardiologia* 1991; 36 (5): 385–390.
2. Berg BW, Dillard TA, Derderian SS. *American Journal of Medicine* 1993; 94: 407–412.
3. Blumen IJ, Abernethy MK, Dunne MJ. *Critical Care Clinics* 1992; 8: 597–618.

Table 12 Values expressed as mean (SD). CP = cabin pressure (ft); Sp_{O_2} = Oxygen saturation (%); SD = stroke distance (cm); MAP = mean arterial pressure (mm Hg); SVR = systemic vascular resistance (mm Hg cm^{-1}); MD = minute distance (cm). *a*: *vs* baseline value. *b*: *vs* take-off value. *c*: *vs* descent value ($P < 0.05$)

	Baseline	Take off	Air	Descent
CP	Ground	2000	5000–8000	3000
Heart rate	71 (25)	74 (18)	72 (15)	70 (13)
Sp_{O_2}	97 (2)	96 (2)^{a}	94 (2)^{ab}	96 (2)
SD	24 (9)	28 (10)^{ac}	27 (8)	24 (6)
MAP	88 (14)	78 (9)^{a}	79 (10)^{a}	80 (10)^{a}
SVR	6.1 (2.2)	4.2 (1.4)^{a}	4.3 (1)	4.9 (0.7)
MD	1574 (406)	2056 (699)^{ac}	1918 (509)	1662 (305)^{b}

Is the dihydropyridine binding site on neuronal L-type calcium channels a target for i.v. anaesthetic agents?

K. Hirota and D. G. Lambert
University Department of Anaesthesia, Leicester Royal Infirmary, Leicester

Previous work from our group has implicated the voltage sensitive calcium channel as a potential target site for i.v. anaesthetic agents [1, 2]. Moreover, there are conflicting reports as to the interaction of anaesthetic agents with neuronal L, N, T or P channels [3]. In an attempt to assess the role of L-type voltage sensitive calcium channels in the process of anaesthesia we have examined the interactions of i.v. anaesthetic agents with the L-channel 1,4-dihydropyridine binding site in rat cerebrocortical membranes.

Rat cortical membranes were prepared in 50 mmol litre^{-1} Tris HCl, pH 7.4 by homogenization and centrifugation. Binding assays were performed in 1 ml volumes of 50 mmol litre^{-1} Tris HCl, pH 7.4 for 90 min at room temperature using approximately 200 µg of protein. Non-specific binding was defined in the presence of 10 µmol litre^{-1} nifedipine and bound and free radioactivity were separated by vacuum filtration. Total number of binding sites (Bmax) and the binding affinity (K_d) were determined by incubating with increasing concentrations (approx. 0.02–2 nmol litre^{-1}) of the dihydropyridine [^{3}H]PN200-110. The effects of anaesthetics were determined by displacing a fixed (0.2 nmol litre^{-1}) concentration of [^{3}H]PN200-110, and the concentration of anaesthetic producing 25 and 50% displacement were corrected for the competing mass of [^{3}H]PN200-110 to yield K_{25} and K_{50}.

The binding of [^{3}H]PN200-110 was dose dependent and saturable with a K_d and Bmax of 59 (5) pM and 152 (14) fmol mg^{-1} protein (mean (SEM), $n = 5$) respectively. With the exception of ketamine all other agents tested showed some interaction with the 1,4-dihydropyridine binding site (table 13).

Although these data supported the general hypothesis that i.v. anaesthetic agents interact with L-type voltage sensitive calcium channels, ketamine appeared inactive. Studies currently under way will determine if these interactions are more marked with a more physiologically relevant model, i.e. depolarized neuronal cells.

Table 13 Effects of i.v. anaesthetic agents on [^{3}H]PN200-110 binding. (Data are mean (SEM). *For both racemic and resolved)

Agent	n	K_{25} (µmol litre^{-1})	K_{50} (µmol litre^{-1})
Thiopentone	6	48±2	134±6
Pentobarbitone	6	95±7	211±6
Propofol	6	40±2	97±5
Etomidate	6	27±2	69±5
Ketamine*	4	> 1000	> 1000

Key words

Anaesthetics, i.v. Ions, ion channels. Ions, calcium. Model, rat. Brain, cerebral cortex.

Acknowledgements

We thank Zeneca, Parke-Davis, Rhone-Poulenc-Rorer and Janssen-Cilag for providing pure propofol, ketamine isomers, thiopentone and etomidate respectively.

References

1. Lambert DG, Atcheson R, Frost CL, Rowbotham DJ. *British Journal of Anaesthesia* 1994; 73: 271P.
2. Sikand K, Smith G, Lambert DG. *Biochemical Society Transactions* 1995; 23: 417S.
3. Lynch C, Pancrazio JJ. *Anesthesiology* 1994; 81: 1–5.

Investigation into the effects of midazolam and propofol on human respiratory cilia beat frequency *in vitro*

H. C. L. Hann and J. H. Raphael
University Department of Anaesthesia, Leicester Royal Infirmary, Leicester

Patients on intensive care receiving intermittent positive pressure ventilation (IPPV) are at risk of developing a chest infection primarily owing to the loss of the cough reflex. To facilitate IPPV it is usually necessary to administer sedative agents, the most frequently used being midazolam and propofol. Related drugs have been shown to impair mucociliary clearance (MCC) [1], an important defence against respiratory infections.

We have investigated the effect of midazolam and propofol on human respiratory cilia beat frequency (CBF), an important determinant of MCC, using the transmitted light technique [2]. Nasal turbinates from 16 patients who had undergone turbinectomy for a primary diagnosis of tissue hypertrophy were used as the source of ciliated epithelium. Ciliated discs, 4 mm in diameter, cut from these turbinates were divided into four groups; one group was exposed to midazolam 20 µmol litre^{-1}, a second group was exposed to propofol 70 µmol litre^{-1} and the final two groups acted as matched controls. The ciliated discs were mounted in modified, specially designed perfusion chambers [3] at 37 °C and connected to a control reservoir containing Hanks' balanced salt solution. The samples were perfused for 30 min, after which time a set of baseline readings of CBF were made (T30). One chamber was then connected to a reservoir containing the drug solution and measurements of CBF were made at T60 and T120 min. The drug exposure was then stopped and a final set of CBF measurements were made at T150 min. The investigator was unaware of which chamber had been exposed to the drug.

Mean CBF (SEM) Hz data for each time point in each experimental group are shown in table 14.

Statistical analysis was performed using MANOVA for repeated measures. Significance was taken at $P < 0.05$ (midazolam, $P = 0.212$; propofol, $P = 0.310$).

We concluded that at the concentrations used in this experiment, there were no significant effects of midazolam or propofol on human respiratory cilia beat frequency *in vitro*.

Table 14 Mean cilia beat frequency (SEM) Hz

Time (min)	Propofol	Control	Midazolam	Control
T30	13.7 (0.7)	11.8 (0.7)	13.8 (0.3)	13.7 (0.3)
T60	12.5 (0.6)	11.2 (0.8)	12.9 (0.3)	14.0 (0.2)
T120	13.6 (0.4)	12.0 (0.6)	13.0 (0.2)	12.9 (0.3)
T150	11.3 (0.7)	11.0 (0.6)	13.8 (0.3)	11.9 (0.3)

Key words

Lung, pathophysiology. Hypnotics benzodiazepines, midazolam. Anaesthetics i.v., propofol.

References

1. Hasani A, Spiteri MA, Pavia D, Lopez-Vidriero MT, Agnew JE, Clarke SW. *Thorax* 1992; 47: 298–300.
2. Teichtahl H, Wright PL, Kirsner RLG. *Medical and Biological Engineering and Computing* 1986; 24: 193–196.
3. Braga PC, Bossi R, Allegra L. *Methods and Findings in Experimental Clinical Pharmacology* 1986; 8 (5): 321–326.

Morphine consumption in patients receiving rectal paracetamol and diclofenac alone and in combination

J. E. Montgomery*, I. G. Kestin, J. R. Sneyd and C. J. Sutherland*
Department of Anaesthesia, Derriford Hospital, Plymouth

Diclofenac is frequently used after major surgery in combination with morphine to enhance analgesia and reduce morphine-related side effects [1]. The efficacy of paracetamol in combination with morphine has not been established and as paracetamol and diclofenac have different mechanisms of action their effects may be additive. We have undertaken a randomized, double-blind, trial to assess the effects of paracetamol and diclofenac alone, and in combination, on postoperative morphine use.

Sixty patients, ASA grade I or II, scheduled for elective abdominal gynaecological surgery gave written informed consent. After premedication with temazepam patients were anaesthetized with thiopentone, morphine up to 0.2 mg kg^{-1} i.v., vecuronium, nitrous oxide and enflurane. Residual neuromuscular block was antagonized with glycopyrrolate and neostigmine. After induction of anaesthesia and before surgery patients were given suppositories of either 1.5 g paracetamol (P), $n = 20$, or 100 mg diclofenac (D), $n = 20$, or a combination of 1.5 g paracetamol and 100 mg diclofenac (C), $n = 20$. In recovery the patients received further boluses of i.v. morphine if required and were then given a patient-controlled analgesia system (PCA) programmed to give a bolus of 1 mg of morphine with 50 μg droperidol, a 5-min lockout and no background infusion. Cumulative morphine use was recorded at hourly intervals for 24 h.

One patient in group C was excluded from the analysis as she was unable to use the PCA owing to intractable vomiting. Morphine consumption was greatest in group P and lowest in group C (fig. 9).

Paracetamol may augment diclofenac analgesia. However, a larger study is needed to test this hypothesis.

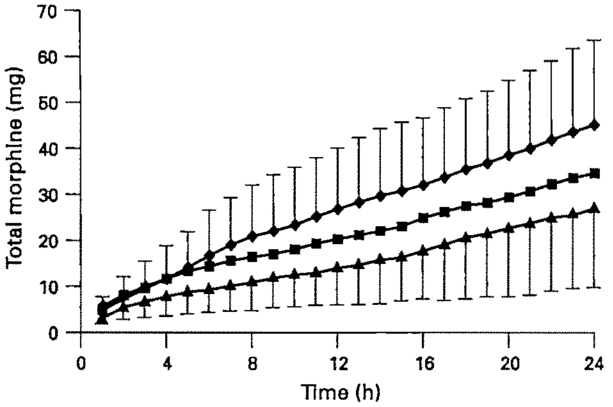


Figure 9 Morphine consumption, mean (SD). For clarity group D (■, diclofenac) error bars are omitted. The difference in morphine consumption between groups P (◆, paracetamol) and C (▲, paracetamol and diclofenac) is significant from 6 to 24 h, $P < 0.05$ ANOVA.

Key words

Analgesics opioid, morphine. Analgesics non-opioid, diclofenac. Analgesics non-opioid, paracetamol.

Reference

1. Hodson NBA, Burns J, Blyth A, Kenny GNC, McArdle CS. *Anaesthesia* 1987; 42: 1005–1008.

Effects of desflurane and isoflurane on splanchnic microcirculation during surgery

H. O'Beirne and M. C. Bellamy

Departments of Anaesthesia and Intensive Care, St James's University Hospital, Leeds

Isoflurane has been considered the agent of choice where preservation of splanchnic blood flow is required. Liver blood flow and hepatic artery buffer response are known to be maintained better in the presence of isoflurane than other volatile agents. Effects of desflurane have not been assessed in humans. We have, therefore, compared effects of isoflurane and desflurane anaesthesia on small bowel and hepatic microcirculatory flow during major surgery in humans using laser Doppler flowmetry.

Ethics Committee approval was obtained for this prospective randomized single-blind crossover study. Ten adult patients undergoing major upper abdominal surgery gave informed consent. After premedication with temazepam 20 mg, anaesthesia was induced with thiopentone 3 mg kg^{-1} and fentanyl 3 μg kg^{-1}. Neuromuscular block was facilitated by infusion of atracurium. Patients were randomized to receive desflurane or isoflurane (1 MAC) in oxygen-enriched air. Lungs were ventilated to normocapnea. Steady-state jejunal and liver blood flow in segment III or IV were assessed by laser Doppler flowmetry at steady state (after 30 min inhalation of agent and F_{I}agent/expired agent < 1.1). Volatile anaesthetics were then interchanged, and measurements repeated at steady state. Data were analysed using paired Wilcoxon rank sum test and multiple regression analysis.

Results are expressed as median (interquartile range). There were no differences in MAP, CVP or heart rate between periods breathing the two volatiles (table 15).

We have shown that during major surgery in humans, desflurane anaesthesia at 1 MAC was associated with significantly greater gut blood flow than 1 MAC isoflurane. These differences could not be explained by overall haemodynamic differences. Gut blood flow accounted for 85% of the variability in liver blood flow. This suggested that liver blood flow in this model was largely portal in derivation. The lack of difference in total hepatic flow between groups implied an intact hepatic artery buffer response. These results may have important implications for anaesthesia in high-risk surgical patients.

Table 15 Multiple regression described liver blood flow as (1.3 × gut blood flow) − 24, $P < 0.0001$, $r^2 = 0.85$

	Median blood flow (IQ range) perfusion unit	P value
Gut		
isoflurane	94 (75–154)	0.02
desflurane	186 (146–262)	
Liver		
isoflurane	137 (58–168)	0.26
desflurane	175 (54–453)	

Key words

Blood, flow, splanchnic. Anaesthetics volatile, desflurane.

Effect of cooling on the force of contraction of rat and guineapig phrenic nerve hemidiaphragm preparations

A. J. England, K. Richards and S. A. Feldman

The John Hammond Department of Anaesthesia, East Surrey Hospital, Redhill and The Magill Department of Anaesthesia, Chelsea and Westminster Hospital, London

Previous researchers observed that cooling increases the force of contraction elicited from rat and hamster neuromuscular preparations. However, at temperatures below 10 °C failure of contraction with indirect but not direct stimulation occurs [1]. In evolutionarily more sophisticated animals, such as the dog and humans, the threshold at which the force of neuromuscular contraction starts to decrease with indirect stimulation is close to normal body temperature [2, 3]. This experiment was performed to compare the neuromuscular responses during cooling of the guineapig phrenic nerve hemidiaphragm with those of the rat.

Phrenic nerve hemidiaphragm preparations from freshly killed (carbon dioxide asphyxiated) male Wistar rats (300–400 g) or male Dunkin Hartley guineapigs (300–400 g) were suspended in Kreb's solution maintained at 37 °C. They were pretensioned to 8 *g* and, after stabilization, either indirect or direct supramaximal square wave stimuli were applied. The isometric force of contraction was measured at 5 °C intervals between 17 °C and 37 °C. The force of contraction at 37 °C was referenced as 100% for each experiment and the percentage change in force with temperature was calculated. The mean (SE) referenced force at each temperature was calculated. The changes in referenced force of contraction with temperature was calculated using linear regression (SE).

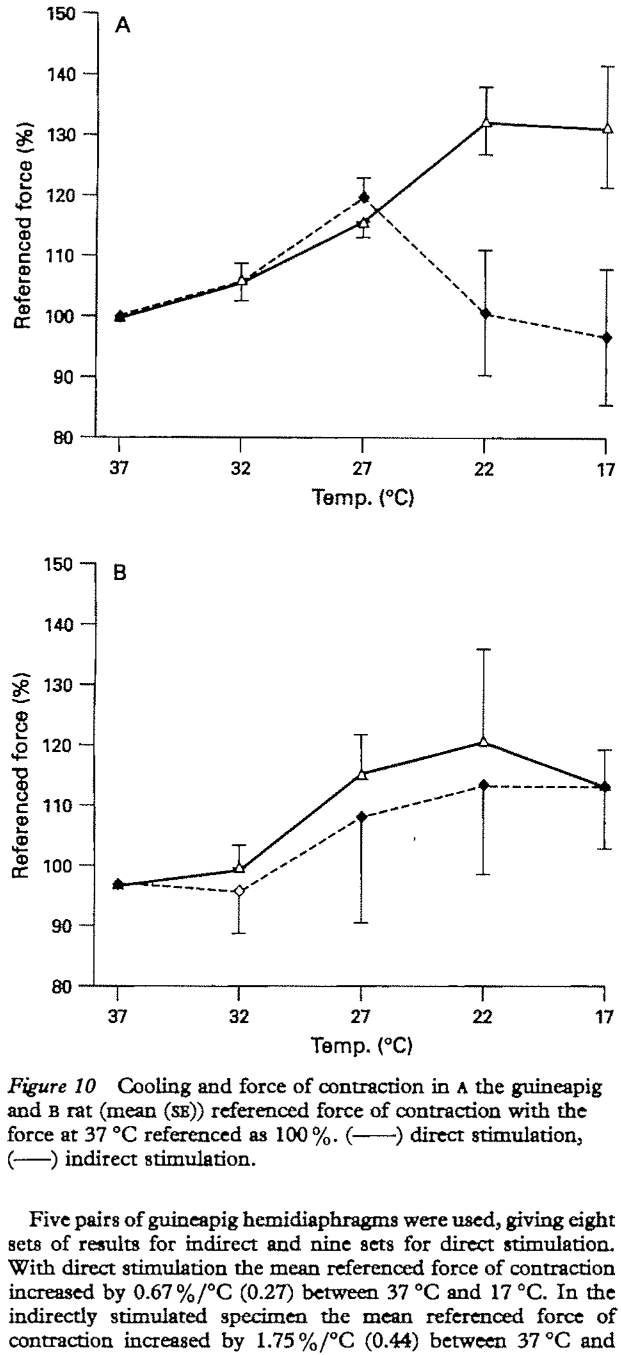


Figure 10 Cooling and force of contraction in A the guineapig and B rat (mean (SE)) referenced force of contraction with the force at 37 °C referenced as 100 %. (——) direct stimulation, (——) indirect stimulation.

Five pairs of guineapig hemidiaphragms were used, giving eight sets of results for indirect and nine sets for direct stimulation. With direct stimulation the mean referenced force of contraction increased by 0.67 %/°C (0.27) between 37 °C and 17 °C. In the indirectly stimulated specimen the mean referenced force of contraction increased by 1.75 %/°C (0.44) between 37 °C and 27 °C, but between 27 °C and 17 °C the force of contraction fell by −1.75 %/°C (1.08).

Five pairs of rat hemidiaphragms were used, giving six sets of results for indirect and light sets for direct stimulation. Between 37 °C and 17 °C the mean referenced force of contraction increased by 1.2 %/°C (0.25) in the direct and 1.1 %/°C (0.34) in the indirectly stimulated specimens.

Cooling to 17 °C enhanced directly and indirectly elicited force of contraction in the rat phrenic nerve diaphragm preparation predominantly by an increased contractility in the muscle. In a similar guineapig preparation moderate hypothermia also enhanced muscle contractility. However, below a threshold at about 27 °C failure of transmission of indirectly applied stimuli developed. This threshold lies at a temperature intermediate between that found by other researchers for the rat and hamster (below 10 °C) [1] and that for the dog [2] and humans [3] (above 32 °C) (fig. 10).

Key words

Complications, hypothermia. Rat. Guineapig. Neuromuscular transmission.

References

1. South FE. *American Journal of Physiology* 1961; **200**: 565–571.
2. Thornton RJ, Blackeney C, Feldman SA. *British Journal of Anaesthesia* 1976; **48**: 264.
3. Heier T, Caldwell JE, Sessler DI, Kitts JB, Miller RD. *Anesthesiology* 1989; **71**: 381–384.

Use of regional i.v. morphine analgesia in patients undergoing total knee arthroplasty

A. R. CORBETT AND J. WISNEWSKI
Department of Anaesthesia, Fremantle Hospital, Fremantle, Western Australia, Australia

While there is substantial experimental evidence [1] for the existence of peripheral opioid receptors the studies looking at clinical applications have been equivocal. Feldman, in an anecdotal report, described decreased postoperative pain after i.v. regional morphine analgesia in major knee surgery [2]. This randomized double-blind placebo controlled study was designed to evaluate any improvement in postoperative analgesia using this technique.

Twenty-four ASA grade I, II or III patients undergoing elective unilateral total knee arthroplasty under tourniquet control were studied. Patients were allocated randomly to two groups. Group A received 50 ml of normal saline (placebo), group B received 5 mg of morphine in 50 ml normal saline. Patients with a previous history of reaction or hypersensitivity to morphine or other opioid derivatives were excluded.

After induction of general anaesthesia using a standard regimen a 22-gauge cannula was inserted into a dorsal foot vein aseptically. The limb was exsanguinated and an arterial tourniquet inflated to 350 mm Hg. The test solution was injected and the cannula removed. Anaesthesia was maintained with isoflurane and nitrous oxide with incremental vecuronium and fentanyl as required.

In the recovery room the patient received 1 mg i.v. boluses of morphine until they were pain-free and then patient-controlled analgesia (PCA) was used for the first 48 h. This provided a 1-mg bolus of morphine with a lockout time of 5 min. Analgesic requirements and visual analogue scores (VAS) were recorded at 0, 0.5, 1, 2, 4, 6 h and every 6 h thereafter. PCA was discontinued when clinically indicated.

Patient groups were well matched for demographic data and technical factors affecting postoperative pain. Eleven patients received placebo, 10 received morphine. Two patients were withdrawn from the control group, one owing to inability to use PCA and the other to incomplete data collection. One patient was withdrawn from the morphine group for surgical reasons.

There were no significant differences between the mean dose of intraoperative fentanyl, 240 µg (175–300 µg) in the placebo group and 257.5 µg (150–375 µg) in patients receiving morphine, or nurse-administered morphine 3.9 mg (0–11 mg) and 3.3 mg (0–10 mg) respectively.

Analysis of the results found no significant differences between the VAS pain scores or in the amount of PCA morphine used (table 16).

Table 16 Patient-controlled morphine dose (mean (SD))

	Time (h)				
	6	12	24	36	48
Placebo group (mg)	15.5 (4.68)	22.0 (7.32)	35.7 (13.71)	47.2 (21.60)	61.0 (38.05)
Morphine group (mg)	19.5 (6.31)	25.6 (9.42)	49.1 (20.11)	69.3 (26.89)	84.3 (27.54)

This study found i.v. regional anaesthesia with 5 mg of morphine did not decrease the pain scores or requirement for postoperative analgesia in patients undergoing total knee replacement.

Key words
Receptors, opioid. Analgesic techniques, regional. Analgesics, opioid, morphine. Surgery, orthopaedic.

References

1. Stein C. *Anesthesia and Analgesia* 1993; **76**: 182–191.
2. Feldman S. *Anaesthesia* 1993; **48**: 171 (Letter).

The following paper was omitted from the last meeting of the ARS in Sheffield. 'Non-steroidal analgesia or patient-controlled analgesia postoperatively?' J. A. Jackson and A. S. Laurence, Department of Anaesthetics, Royal Preston Hospital, Preston.

British Journal of Anaesthesia 1996; **76**: 595–598

CORRESPONDENCE

Psychological characteristics and patient-controlled analgesia

Sir,—Dr McConaghy writes [1] requesting clarification of some aspects of our study of psychological characteristics and patient-controlled analgesia [2]. We are grateful to Dr McConaghy for his appreciation of the importance of our findings for anaesthetists involved in the management of acute postoperative pain. He suggests that the anaesthetic technique may have been insufficiently standardized because "the analgesic component consisted of either fentanyl or papaveretum, together with an opioid premedicant (either pethidine or papaveretum)" and that the timing of intraoperative opioid may have affected consumption of postoperative analgesics. Further, he suggests that we chose to compare an inefficient i.m. regimen when an hourly "as required" regimen has been shown to be safe and effective [3]. With regard to premedication, as stated in the article, the majority (90 of 110) of patients received temazepam and some of the remainder received lorazepam; the few patients who received opioid premedication were approximately equally distributed between the groups, and therefore it is unlikely that this had any significant effect in this fairly large study. They received opioids because of occasional preoperative assessment by trainee anaesthetists who had been taught to use opioids during their previous appointments.

The other concerns are appropriate but must be viewed in the context of when and where this study was performed. It was for this reason that we gave the dates (1988–90) of the study. In planning the study it was necessary to obtain the co-operation of the career anaesthetists who regularly anaesthetized such patients. In a district hospital without a major research programme, individual clinicians are unaccustomed to modifying their clinical techniques in the interests of research. Two consultants were unable to agree: one because the study required that patients would not know before operation what pain relief regimen they would be prescribed, the other because it was his practice to use trichlorethylene for intraoperative analgesia–anaesthesia and he was not prepared to change to either fentanyl or papaveretum. The other anaesthetists normally used either fentanyl or papaveretum as a bolus dose immediately after induction of anaesthesia, with occasional increments if indicated clinically during the procedure. We felt that these techniques were sufficiently alike, together with randomization of patients, to ensure the absence of bias.

The problem of the effectiveness of the standard 4-hourly i.m. regimen is somewhat similar. For many years one of us has advocated shorter intervals but, at the time the study was planned (early 1988), colleagues were unwilling to change. Ethics Committee approval was obtained on the basis of the two regimens in routine use in the hospital. Our judgement was confirmed by the Cardiff study [3] but this was published long after our study was complete.

V. J. Thomas
Department of Nursing Studies
King's College London
M. Heath
Directorate of Anaesthesia and Pain Relief
Lewisham Hospital NHS Trust
London

1. McConaghy PM. Psychological characteristics and patient-controlled analgesia. *British Journal of Anaesthesia* 1995; **75**: 376.
2. Thomas V, Heath M, Rose D, Flory P. Psychological characteristics of patients and the effectiveness of patient-controlled analgesia. *British Journal of Anaesthesia* 1995; **74**: 271–276.
3. Gould TH, Crosby DL, Harmer M, Lloyd SM, Lunn JN, Rees GAD, Roberts DE, Webster JA. Policy for controlling pain after surgery: effect of sequential changes in management. *British Medical Journal* 1992; **305**: 1187–1193.

Ulnar and common peroneal nerve block revisited

Sir,—There has been much recent discussion in this journal on the incidence and mechanisms of nerve injury after local anaesthetic block [1, 2]. However, little attention has focused on particular blocks. After discussions of the advantages and disadvantages of ulnar nerve block at the elbow and common peroneal nerve block at the head of the fibula, we decided to investigate the evidence for and against these two nerve blocks.

It is commonly taught that the ulnar nerve should not be blocked at the elbow. The nerve is palpable as it runs around the medial epicondyle and is easily accessible at this point. However, it is said to be protected by a thick fibrous epineurium and therefore intraneural injection may be required to allow adequate axonal block, risking neuritis. Some standard texts reinforce this view. Bridenbaugh states: "block of the ulnar nerve at the elbow is often said to lead to residual neuritis" [3]. This is similarly described by Löfström [4]. Likewise, the common peroneal nerve is easily palpable at the head of the fibula and for similar reasons it is stated that block at this landmark carries a "considerable risk of post-anaesthetic neuritis" [5]. However, elsewhere these risks are not mentioned and the blocks described at these sites [6].

This variation in advice prompted us to carry out a comprehensive literature search to identify case reports of nerve damage after the two blocks. A Medline search back to 1966 revealed no case reports of ulnar or common peroneal neuropathy after block at the elbow or head of fibula. We then searched through textbooks on regional anaesthesia dating back to 1922 and could find no reports of such neuropathies. In fact the earlier texts described how to perform these blocks [7]. Furthermore, neuropathies are relatively common after anaesthesia and surgery and have been reviewed extensively, providing information on their aetiology. Ulnar neuropathy is the most common mononeuropathy in this situation and a study of closed malpractice claims by the American Society of Anesthesiologists found 77 cases of ulnar neuropathy from a total of 227 cases of nerve damage [8]. In the majority of cases the causative mechanism was unknown. Regional anaesthesia was uncommon but tended to be central or plexus block, and there was no mention of ulnar nerve block at the elbow. Another retrospective study reviewed the postoperative courses of 1129692 surgical patients undergoing non-cardiac surgery and found 414 cases of ulnar neuropathy [9]. This was associated with male gender, abnormally high or low body mass index and prolonged hospital stay. It was not associated with regional anaesthesia in general or ulnar nerve block in particular.

It would be wise to perform these blocks meticulously and only in awake patients to minimize the risk of intraneural injection. However, in this era of evidence-based medicine, there is nothing to support the contention that these nerve blocks are associated with neuritis. Should we therefore disallow ourselves the advantages presented by the convenient anatomy of these nerves?

A. J. Souter
Nuffield Department of Anaesthetics
John Radcliffe Hospital
Oxford
C. J. Glynn
Nuffield Department of Anaesthetics
Churchill Hospital
Oxford

1. Moore DC, Mulroy MF, Thompson GE. Peripheral nerve damage and regional anaesthesia. *British Journal of Anaesthesia* 1994; **73**: 435–436.
2. Chambers WA. Peripheral nerve damage and regional anaesthesia. *British Journal of Anaesthesia* 1992; **69**: 429–430.
3. Bridenbaugh LD. The upper extremity: somatic blockade. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain.* Philadelphia: JB Lippincott, 1988; 408–409.
4. Löfström B. Nerve block at the elbow. In: Eriksson E, ed. *Illustrated Handbook of Local Anaesthesia*, 2nd Edn. London: Lloyd-Luke (Medical Books), 1979; 86–87.

5. Löfström B. Nerve block at the knee-joint. In: Eriksson E, ed. *Illustrated Handbook of Local Anaesthesia*, 2nd Edn. London: Lloyd-Luke (Medical Books), 1979; 111.
6. Scott DB. *Techniques of Regional Anaesthesia*, 1st Edn. Norwalk: Mediglobe, 1989.
7. Labat G. *Regional Anaesthesia, its Technic and Application*, 2nd Edn. Philadelphia: WB Saunders, 1922.
8. Kroll DA, Caplain RA, Posner K. Nerve injury associated with anesthesia. *Anesthesiology* 1990; 73: 202–207.
9. Warner MA, Warner ME, Martin JT. Ulnar neuropathy: incidence, outcome, and risk factors in sedated or anesthetized patients. *Anesthesiology* 1994; **81**: 1332–1340.

Nebulized lignocaine before gaseous induction with desflurane

Sir,—I read with interest the recent study by Bunting, Kelly and Milligan [1] illustrating the failure of nebulized lignocaine to suppress airway irritation during gaseous induction with desflurane. The results of this study are alarming, and provide further evidence against the use of desflurane as an induction agent.

However, I am concerned that the authors have failed to document the duration of administration of the nebulized solution (4 % lignocaine or 0.9 % saline), nor formally tested the airway for the absence of reflexes (e.g. gag reflex) before administration of desflurane. It is therefore possible that insufficient time was allowed for the onset of action in those given lignocaine.

While the use of lignocaine in providing topical anaesthesia to the airway has been studied widely, the onset time of nebulized lignocaine is poorly documented. The information available in standard texts suggests an onset time of 5 min or less [2,3]. However, Vuckovic and colleagues [4] administered 4% lignocaine via a nebulizer (4–6 ml in total) for up to 7 min and found that 10% of patients required additional nebulized lignocaine after formal testing of upper airway reflexes. These findings suggest a variable onset of action which can only be proved by the absence of upper airway reflexes.

The "blinded" nature of the authors' study has precluded formal testing of the airway, making any assumption of the efficacy of nebulized lignocaine in decreasing respiratory responses during gaseous induction with desflurane misleading. Allowing sufficient time for verifiable onset of action may yet show this technique to be a useful adjunct to gaseous induction with desflurane.

P. G. Nay
Department of Anaesthesia
St Mary's Hospital
London

1. Bunting HE, Kelly MC, Milligan KR. Effect of nebulized lignocaine on airway irritation and haemodynamic changes during induction of anaesthesia with desflurane. *British Journal of Anaesthesia* 1995; 75: 631–633.
2. Boughton K, Bowes JB. Surface and infiltration anaesthesia. In: Nimmon WS, Smith G, eds. *Anaesthesia, vol. 2.* Oxford: Blackwell Scientific Publications, 1990; 1092–1114.
3. Wood M. Local anesthetic agents. In: Wood M, Wood AJJ, eds. *Drugs and Anesthesia. Pharmacology for Anesthesiologists*, 2nd Edn. Baltimore: Williams and Wilkins, 1990; 319–345.
4. Vuckovic DD, Rooney SM, Goldiner PL, O'Sullivan D. Aerosol anesthesia of the airway using a small disposable nebuliser. *Anesthesia and Analgesia* 1980; 59: 803–804.

Sir,—In our study we did not formally assess upper airway reflexes before induction of anaesthesia with desflurane. The site of initiation of reflexes with desflurane is unknown, but may be the sensitive larynx or smaller airways. We used a nebulizer and oxygen flow rate which produce particles small enough to reach the larynx and smaller airways so that they are not all deposited in the oral cavity and oropharynx. Rapid, simple tests would have permitted assessment of the oral cavity and gag reflex, but not the larynx and respiratory tree in which we were interested. It was not our intention to anaesthetize the airway completely, as for intubation, but to administer doses which, when given by nebulizer, have been shown to obtund circulatory responses to laryngoscopy and reduce respiratory responses to airway irritation. Assessment of upper airway reflexes may have caused airway irritation before induction of anaesthesia, particularly in the control group, and may therefore have influenced the cardiorespiratory responses to induction with desflurane, in which we were interested.

Using a Hudson AVA NEB and an oxygen flow rate of 8 litre min^{-1}, nebulization of 4 % lignocaine 4 ml requires approximately 8 min and 6 ml requires approximately 15 min. Although we cannot be certain that the dose of lignocaine or time for onset of action was adequate in all cases, the work of Vuckovic and colleagues [1] would suggest that these were sufficient in 90 % of cases.

We state that the conclusions regarding the effects of nebulized lignocaine refer only to the dose and method of administration used in this study. It is possible that different techniques and doses of lignocaine would yield better results.

H. E. Bunting
M. C. Kelly
K. R. Milligan
Department of Anaesthetics
Queen's University, Belfast

1. Vuckovic DD, Rooney SM, Goldiner PL, O'Sullivan D. Aerosol anesthesia of the airway using a small disposable nebuliser. *Anesthesia and Analgesia* 1980; 59: 803–804.

Factors governing onset of neuromuscular block

Sir,—Audibert and Donati's article [1] demonstrated the phenomenon first reported by Hood, Campkin and Feldman [2], Campkin and Hood [3], and Feldman [4] that an increase in non-depolarizing block occurs despite cessation of drug delivery from the circulation. Hood, Campkin and Feldman [2] used a 0.1 × ED_{95} drug dose injected into the isolated forearm of conscious volunteers and released the tourniquet during onset at 50 % block. We found that the non-depolarizing blocks progressed to a much greater degree, and over a much longer time scale, than that of decamethonium; the results are shown in figure 1.

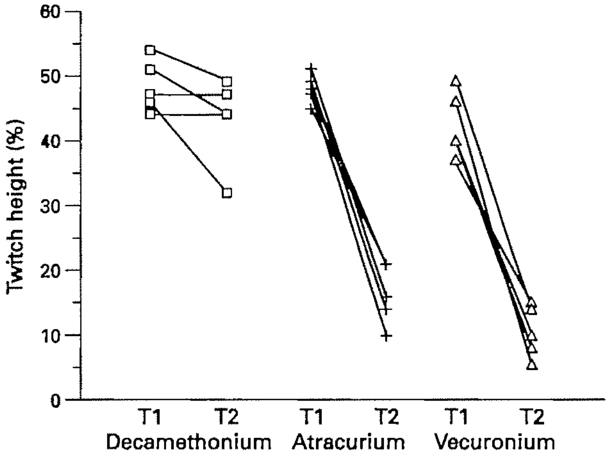


Figure 1 Isolated forearm blocks after decamethonium 0.15 mg, atracurium 2 mg and vecuronium 0.3 mg. These doses produced similar rates of onset before tourniquet release. Mean time courses of the increase in block after tourniquet release were 3.26 (SD 0.24) min for vecuronium, 2.6 (0.43) min for atracurium and less than 4 (4) s for decamethonium.

The isolated forearm is akin to a Bier's block: drug is flushed from the arm after tourniquet release, and recirculation of drug is not the cause of any subsequent increase in block [5]. Audibert and Donati's technique of inflating a tourniquet during onset of systemic block would presumably trap drug-containing blood in the arm. We suggest that transfer of drug from this reservoir would account for some of the subsequent increase in block thereafter and, in particular, that of suxamethonium over approximately 3 min, because intra-arterial administration of agonists reveals little delay in onset of block. While Bartowski and colleagues [6] observed that small doses of intra-arterial vecuronium took 1.39 min to achieve 90 % of maximum effect, Bacq and

Brown [7] found that acetylcholine achieved maximal block in 10 s.

We believe the sum of this previous work contradicts Audibert and Donati's explanation of their results. The suggestion that their observed increase in both suxamethonium and vecuronium block was caused by a common mechanism (drug transfer from the extracellular fluid to the junction) would appear unlikely unless some other differential existed. The likelihood that the two classes of drug achieve effect at very different receptor occupancies does not provide that differential, in our opinion.

The relationship between receptor occupancy and biophase drug concentration is described by a rectangular hyperbola. Non-depolarizing drugs, effective at 80% occupancy, are on the flat part of the curve, while suxamethonium, perhaps effective at less than 10% occupancy, is on the steep part. For equal percentage increases in biophase concentration, the latter has a much greater increase in percentage receptor occupancy than the former. Yet Audibert and Donati found a smaller increase in depolarizing block than non-depolarizing block after cessation of the blood supply to the arm, and we found a more marked difference between the two classes of drug (fig. 1). Some mechanism would appear to exist which produces the difference between the two classes of drug.

Buffered diffusion has been suggested by the authors as the mechanism causing the delay in onset of non-depolarizing drugs. However, it is not clear why depolarizing drugs should not also be subject to this process and so buffered diffusion alone would not appear to explain their shorter onset time occurring from intra-arterial or isolated forearm delivery.

We suggest that non-depolarizing drugs undergo extensive binding in the junction with non-specific biophase binding sites. These provide a reservoir which limits ingress [8] and egress [9, 10] from the junction at a specific rate for each drug. The studied depolarizing drugs do not act in the same way [11] which allows recovery from block with these agents to be affected by blood flow [12].

The authors' important conclusion is that redistribution of drug *within the muscle* may place intrinsic limits on the speed of onset of action of non-depolarizing drugs. Whatever the cause of this delay in transfer of drug between blood and biophase (suggested 25 yr ago [11]) its elucidation will aid the development of a safe non-depolarizing equivalent of suxamethonium.

S. Feldman
J. Hood
Magil Department of Anaesthetics
Chelsea and Westminster Hospital
London

1. Audibert G, Donati F. Onset of neuromuscular block after tourniquet inflation: comparison of suxamethonium and vecuronium. *British Journal of Anaesthesia* 1995; 75: 436.
2. Hood JR, Campkin NTA, Feldman SA. Comparison of the onset of depolarizing *vs* non-depolarizing block after early tourniquet release in the isolated forearm. *British Journal of Anaesthesia* 1993; 70: 480P.
3. Campkin NTA, Hood JR. The isolated arm. *Anaesthetic Pharmacology Review* 1993; 1: 77–80.
4. Feldman S. Update on muscle relaxants. *Journal of Hospital Medicine* 1994; 52: 142–149.
5. Hood JR, Campkin NTA, Feldman SA. No effect of circulating drug upon offset of vecuronium isolated forearm block. *Anaesthesia* 1995; 50: 598–600.
6. Bartowski RR, Wilkerson C, Epstein R, Marr A, Schieren H. Onset of neuromuscular blockade: a comparison of intra-arterial and intravenous vecuronium. *Anesthesia and Analgesia* 1992; 74: S17.
7. Bacq ZM, Brown GL. Pharmacological experiments on mammalian voluntary muscle in relation to the theory of chemical transmission. *Journal of Physiology (London)* 1937; 88: 45–60.
8. Feldman SA, Wu X, England A. Rate of 'onset' and 'offset' of four non-depolarizing neuromuscular blocking drugs. *Anaesthesia* 1995; 50: 510–513.
9. Feldman SA. *Muscle Relaxants*. Philadelphia: WB Saunders, 1979.
10. Feldman S. Neuromuscular block. In: Feldman S, Scurr CF, Paton WDM, eds. *Mechanisms of Drug Action in Anaesthesia*. London: Edward Arnold, 1993; 336–356.
11. Feldman S, Tyrrell MF. A new theory of the termination of action of the muscle relaxants. *Proceedings of the Royal Society of Medicine* 1970; 63: 692–695.
12. Goat VA, Yeung ML, Blakeney C, Feldman SA. The effect of blood flow upon the activity of gallamine triethiodide. *British Journal of Anaesthesia* 1974; 48: 69–72.

Sir,—We thank you for the opportunity to respond to the letter of Feldman and Hood. In our view, there is no contradiction between the results of the isolated arm experiments [1–3], the delay observed after intra-arterial injection of drug [4] and our results [5]. A single explanation can account for all observations. In our article [5], we suggested diffusion of molecules from extrajunctional to junctional sites. Feldman and Hood prefer to talk about a reservoir. Both concepts are essentially the same. They provide for transfer of drug to the neuromuscular junction in spite of interruption of blood circulation. The only assumption that has to be made is that the affinity for this extrajunctional site or for the reservoir is less than the affinity for the neuromuscular junction. As a result, the concentration of the drug increases more rapidly in the extrajunctional sites or reservoir during onset.

In the isolated arm experiments, drug is injected i.v., distal to a cuff inflated above arterial pressure. Diffusion to high affinity sites (the neuromuscular junction) takes longer compared with other sites. If the cuff is released during onset, the concentration of drug at extrajunctional sites (the majority of the tissue) is greater than at the junction. Thus, on release of the tourniquet, transfer of drug from a high concentration area to a low concentration area (the junction) is possible, and neuromuscular block increases. In the intra-arterial injection experiments, drug concentration in plasma is presumed to be zero at all times, except for a large increase during injection. This drug has access to junctional and extrajunctional tissue. At the end of injection, its concentration is less at the junction because the affinity for junctional tissue is greater. Thus, drug is free to move along its concentration gradient, allowing block to increase after injection is finished. In our experiments, where the tourniquet was inflated during onset, the situation was the same. Drug had access, via arterial blood, to both junctional and extrajunctional areas. According to the same logic, the concentration of drug increased more rapidly in the latter. When the tourniquet was inflated, drug transfer occurred between extrajunctional areas and junctional areas, thus increasing neuromuscular block.

The reasons for the different affinity for both sites cannot be elucidated from these experiments, but there are data which give a few hints. Feldman, Xu and England [3] reported that decamethonium, atracurium and vecuronium behaved differently when the tourniquet used in the isolated arm experiments was deflated prematurely. Onset continued for the non-depolarizing drugs, but not for the depolarizing drug. We found the same, using a different mode of drug delivery, and interrupting delivery in a different way. Based on the above explanation, one has to conclude that the affinity of depolarizing drugs for junctional and extrajunctional tissue is approximately the same, while the affinity of atracurium and vecuronium for both types of tissue is different.

Feldman and Hood suggested that non-depolarizing drugs *undergo extensive binding in the junction with non-specific biophase binding sites*. We suggest that these sites need not be non-specific and may be the junctional receptors themselves. Binding of depolarizing drugs would be much less extensive, if they are effective at a lower proportion of receptor occupancy. Also, our hypothesis suggests that, for non-depolarizing drugs, the extent of binding depends directly on potency. This hypothesis was tested in another set of experiments which showed that for rocuronium, a less potent drug than vecuronium or atracurium, block is affected in much the same way as suxamethonium by tourniquet inflation. This result is also explained by the mechanism of buffered diffusion, which predicts that high affinity drugs (potency is a measure of affinity) have a slower onset [6].

G. Audibert
F. Donati
Hôtel-Dieu Hospital
Montréal, Québec, Canada

1. Hood JR, Campkin NTA, Feldman SA. Comparison of onset of depolarizing *vs* non-depolarizing block after tourniquet release in the isolated forearm. *British Journal of Anaesthesia* 1993; 70: 480P.

2. Hood JR, Campkin NTA, Feldman SA. No effect of circulating drug upon offset of vecuronium isolated forearm block. *Anaesthesia* 1995; 50: 598–600.
3. Feldman SA, Wu X, England A. Rate of onset and offset of four non-depolarizing neuromuscular blocking drugs. *Anaesthesia* 1995; 50: 510–513.
4. Bartkowski RR, Wilkerson C, Epstein R, Marr A, Schieren H. Onset of neuromuscular blockade: a comparison of intra-arterial and intravenous vecuronium. *Anesthesia and Analgesia* 1992: 74: S17.
5. Audibert G, Donati F. Onset of neuromuscular block after tourniquet inflation: comparison of suxamethonium with vecuronium. *British Journal of Anaesthesia* 1995; 75: 436–440.
6. Law-Min JC, Bekevac I, Glavinovic MI, Donati F, Bevan DR. Iontophoretic study of speed of action of various muscle relaxants. *Anesthesiology* 1992; 77: 351–356.

Effects of propofol and isoflurane on right ventricular function

Sir,—We read with interest the article by Kellow and colleagues [1]. It would appear that they have not noticed our article [2] published over a year ago, which also studied the effects of propofol and isoflurane on right ventricular function. Interestingly we came to the opposite conclusion. Using a within-patient crossover design, we found that cardiac index and right ventricular ejection fraction were significantly higher when propofol was given for maintenance of anaesthesia compared with isoflurane. We found no differences in end-systolic volume index between the two agents, but agree with Kellow's study that end-diastolic volume was significantly higher with propofol. The differences in results probably reflect differences in the experimental design, although it is not possible to exclude differences in the populations studied.

In all studies comparing the effects of two anaesthetic agents on the function of a specific organ it is vital that equipotent or equivalent anaesthetic doses of the two agents are used for the comparison. Furthermore, comparisons must only be made when steady state anaesthesia with these equipotent doses has been achieved. Kellow and colleagues seem to have compared two "...generally accepted techniques...", whereas we took considerable care to compare similar anaesthetic doses of propofol and isoflurane, by using the same numerical values of minimal infusion rate for propofol and minimal alveolar concentration for isoflurane for each patient [3].

It is particularly important that observations on cardiac function are made during periods of steady state anaesthesia. It is likely that plasma concentrations of isoflurane and propofol were not constant for the measurement times in the current study. It is known that the inspired concentration of a volatile agent does not have a relationship to blood or brain concentrations, without taking into account other factors, particularly time. It appears from the study design that a constant inspired concentration of isoflurane was given throughout. This is likely to have resulted in greater brain concentrations of isoflurane at the end of operation than at the first datum point 20 min after starting isoflurane, implying that isoflurane concentrations and anaesthetic depth were not constant in the isoflurane group throughout the study. Similarly, kinetic models for plasma concentrations of propofol related to infusion rate take into account the age and weight of the subject [4]. In Kellow's study it appears that the age of the patient was not considered in controlling the propofol infusion rate, and no attempt was made to estimate plasma concentrations which continue to increase if a constant infusion rate is used. Consideration of both of these effects are accepted techniques for propofol infusion regimens [4].

Finally, and perhaps most importantly, in any study considering right ventricular function, it is vital that venous preload is standardized, and the same, in both groups, and that these filling pressures are maintained throughout the study. It is generally accepted practice to use right atrial pressure as a measure of preload. The authors did have this information available, as they were using a REF-1 pulmonary artery catheter, but they have not presented the data. Interestingly they gave only the changes in end-diastolic volume. In our study we have shown this to change, despite constant filling pressure, as compliance changed in response to propofol. Using end-diastolic volume, although there were no differences within each group over time, there were significant differences between the groups. Therefore, comparisons of cardiac function between the groups may not be appropriate.

We agree that it is difficult to compare two anaesthetic agents, particularly when they are given by different routes. Kellow's study showed that with the procedure used, propofol and isoflurane have different effects on right ventricular function. However, the experimental conditions may not have been equivalent for each agent, because of the difficulty in comparing the anaesthetics, and lack of standardization of anaesthetic administration over time and right ventricular filling pressures. We suggest that their study regimen may not have been appropriate to compare these two anaesthetic agents.

O. Boyd
R. M. Grounds
St George's Hospital
Tooting, London

1. Kellow NH, Scott AD, White SA, Feneck RO. Comparison of the effects of propofol and isoflurane anaesthesia on right ventricular function and shunt fraction during thoracic surgery. *British Journal of Anaesthesia* 1995; 75: 578–582.
2. Boyd O, Murdoch LJ, Mackay CJ, Bennett ED, Grounds RM. The cardiovascular changes associated with equipotent anaesthesia with either propofol or isoflurane, with particular emphasis on right ventricular function. *Acta Anaesthesiologica Scandinavica* 1994; 38: 357–362.
3. Prys-Roberts C. Cardiovascular effects of continuous intravenous anaesthesia compared with those of inhalational anaesthesia. *Acta Anaesthesiologica Scandinavica* 1982; 26: 10–17.
4. White M, Kenny GNC. Intravenous propofol anaesthesia using a computerised infusion system. *Anaesthesia* 1990; 45: 204–209.

ERRATUM

British Journal of Anaesthesia 1995; 75: 274–278

p. 279. In the paragraph headed "Patient-related factors", the sentence beginning "However, we did not investigate the possible interference of other factors, such as the dose of local anaesthetic............block, should read "However, *the authors [10]* did not investigate the possible interference of other factors, such as the dose of local anaesthetic............block.

We apologize to the authors for this confusion which arose during the editorial process.

British Journal of Anaesthesia 1996; **76**: 599

BOOK REVIEWS

Neuro-anaesthetic Practice. H. VAN AKEN (editor). Published by BMJ Publishing Group, London. Pp. 305; indexed; illustrated. Price £29.95.

This book forms part of a series on fundamentals of anaesthesia and acute medicine published by the BMJ publishing group. It is priced very competitively compared with other books on neuroanaesthesia intended for trainees preparing for examinations, and established neuroanaesthetists wishing to update their knowledge.

The chapters are written by contributors from several centres in Europe and North America, and include physiology and metabolism of the central nervous system, neurological diseases in the intensive care unit, radiological study of lesions of the central nervous system, anaesthetic agents, fluid management in neurological patients, intraoperative and postoperative monitoring of the CNS for neurosurgery, intraoperative and postoperative positioning of the neurosurgical patient, anaesthetic management of aneurysms and arteriovenous malformations, anaesthetic conditions for specific neurosurgical procedures, management of acute head injury and brain protection, and brain death.

The majority of chapters are well written and provide a good review of the subject matter, but there are several spelling mistakes and factual inaccuracies which spoil the flow of the text and may confuse the reader. A better title for chapter 2 would be "Neurological diseases encountered by neuroanaesthetists". This chapter is too long and I question the need to include details on fixation of pathology specimens and histological changes associated with ischaemia. However, the description of tumours and their classification provides a good reference source for neuroanaesthetists. The chapter on radiology is pitched at the right level for trainee and established neuroanaesthetists but anaesthetic considerations are not discussed. The reasons for including a chapter on intraoperative and postoperative positioning are not clear because this topic could be dealt with more effectively in the chapters on anaesthetic management of the various neurosurgical procedures. The chapter on anaesthetic considerations for specific neurosurgical procedures lacks sufficient detail for preparation for examinations or for reference purposes. In particular, the stages of spinal shock and hyperreflexia after spinal cord transection are not differentiated clearly.

This book provides good up-to-date reviews of many areas of neuroanaesthetic practice which established practitioners with an interest in neuroanaesthesia and neurointensive care will find useful. It is less suitable for trainee anaesthetists preparing for examinations because it is too detailed in some areas and lacks important details and accuracy in others. Although considerably more expensive, ***Anaesthesia and Intensive Care for the Neurosurgical Patient*** gives a better overview of the subject for the trainee preparing for the part 3 FRCA examination.

E. Moss

Intensive Care: A Concise Textbook, 2nd Edn. C. J. HIND AND D. WATSON. Published by W. B. Saunders, London. Pp. 477; indexed; illustrated. Price £29.95.

This book is aimed at doctors in training, both as an introduction to the practice of intensive therapy for anaesthetists and also for surgical or general medical trainees who are increasingly expected to have an understanding of the principles of management of the critically ill patient. This is a difficult task for a book of this size, but one that it achieves admirably.

The authors have drawn on the talents of several other experts, all working in the UK, to produce a well organized, concise and informative book. The text is supplemented with clear diagrams, tables and radiographs. The index is comprehensive and there are ample references at the end of each chapter. This book also includes brief, illustrated advice on the practical techniques of radial artery cannulation and placement of internal jugular catheters and chest drains.

The first chapter, "Planning, organizing and management", might have been titled better, as it includes the equally important topics of outcome and severity scoring systems. Many of the 20 chapters cover individual organ systems, such as the gastrointestinal and endocrine systems, but there are also separate chapters on infection, trauma, poisoning, the obstetric patient, disturbance of body temperature and transport of the critically ill. In addition, there are excellent chapters devoted to shock, applied cardiovascular and respiratory physiology, and assessment and monitoring of these systems, including the newer non-invasive investigations of cardiac function. The section dealing with sources of error in intra-arterial monitoring could perhaps have been expanded to include greater discussion on critical damping.

The chapter on "General aspects" is perhaps the only weak area in this book; it covers the often neglected topics of nutritional support, which probably deserves a chapter on its own, and sedation. Other important areas such as stress ulceration and thromboembolism are also covered here. The latter topic would have benefited from more discussion on the difficulty of diagnosing pulmonary embolism in the critically ill patient.

However, these are only minor criticisms of an excellent book. It achieves exactly what its authors set out to do. It will also be very useful for consultants when they are preparing tutorials and teaching sessions for trainees. Anaesthetic trainees should consider it essential reading and it deserves a place in every intensive therapy unit's library.

R. Wenstone

Handbook of Neonatal Anaesthesia. D. G. HUGHES, S. J. MATHER AND A. R. WOLF (editors). Published by W. B. Saunders, London. Pp. 387; indexed; illustrated. Price £22.50.

It is widely accepted that neonatal anaesthesia should be carried out only in hospitals that have the necessary specialized facilities and staff. It is perhaps unfortunate that it is not until page 165 of this handbook that the need for such specialist facilities is mentioned, and that at least one of the contributors appears to condone the practice of occasional neonatal anaesthesia. The book does, however, succeed in tackling the difficult task of presenting the essentials of such a specialized subject. Despite its small (approximately A5 size) format, its 15 chapters present well balanced coverage of both general principles and practice. Topics covered include physiology and pharmacology, general and regional techniques for most aspects of neonatal surgery, including cardiac surgery, monitoring, postoperative respiratory management, transport and resuscitation. Although most of the authors are British, others come from France, Canada, South Africa and the USA, and there is an interesting view from the developing countries. The important chapter on specific surgical conditions provides a useful consensus of views from around the world.

It is perhaps not surprising that some topics, such as aspects of physiology, are covered rather superficially, but there are remarkably few omissions. New drugs such as sevoflurane and rocuronium are mentioned, and all chapters are readable and comprehensively referenced. It is slightly irritating to find different doses of drugs such as thiopentone recommended in different chapters, and different formulae for calculating "acceptable blood loss". The suggestion that hypocapnia can be prevented by adding carbon dioxide to the fresh gas flow is not in line with current UK practice, and the recommendation that tracheal tubes should be inserted to the end of the black line, mentioned by several authors, applies only for some makes of tube. Some aspects of the chapter on the very premature infant, such as details of surfactant therapy, are of more value to a neonatologist than an anaesthetist, while elsewhere the intensive care management of congenital diaphragmatic hernia is stated to be beyond the scope of the text. However, many of the chapters are surprisingly comprehensive for a book of this size. Although this handbook does not contain enough detail for the aspiring neonatal anaesthetist, it does provide a useful introduction to the subject. I am sure it deserves a place in departmental libraries, and many anaesthetists will purchase their own copies.

D. J. Hatch

Papers for publication and all editorial communications should be addressed to:
Professor G. Smith,
Editor, British Journal of Anaesthesia,
University Department of Anaesthesia,
Leicester Royal Infirmary,
Leicester LE1 5WW.
Telephone: 0116 247 0141
Fax: 0116 285 4487

All **business communications** should be sent to the Publishers: Professional & Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR.

The GUIDE TO CONTRIBUTORS may be found in the advertisement section of any issue of the journal (pages ii, iv & vi).

Published monthly. Annual subscriptions: Worldwide £156.00; USA only $245.00 (direct orders only). Trainee rate: Worldwide £75.00. Airmail rates on application. ISSN 0007–0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR. Orders in the USA may be sent to Professional and Scientific Publications, PO Box 408, Franklin, MA 02038, USA.

"WIREX" self-binding cases, which hold a complete volume, i.e. 6 months with room for a supplement and annual handbook, are now available. Price UK £14.00 per two binders, Europe £20.00 per two binders (to cover 1 year). Price includes postage and packing. Rest of the World prices on application. Cheque with order to Hethersett Supplies, Mount Bovers Lane, Hawkwell, Essex SS5 4JA, Tel. (01702) 202393.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statements appear in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statements. Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

© Copyright: 1996 *British Journal of Anaesthesia*
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia*, requests for which should be addressed to the **Publishers**.

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge.

British Journal of Anaesthesia 1996; **76**: 601–603

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 76, No. 5 MAY 1996

EDITORIAL I

Perioperative inadvertent hypothermia: what do we need to prevent?

A non-intentional decrease in core temperature is by far the most common perioperative thermal disturbance, resulting from a combination of impaired thermoregulation and exposure to a cold microclimate.

Hypothermia during anaesthesia and surgery is characterized by an initial rapid decrease in core temperature (0.8–1.0 °C) followed by a slow linear decrease [1]. After 3–4 h of anaesthesia, the decrease stabilizes at approximately 34–35 °C, indicating a thermal state where body heat production equals heat loss.

Several studies have shown the immediate and delayed consequences of mild intraoperative hypothermia on organ function, such as excessive sympathetic stimulation [2,3], interference with drug metabolism [4], modified platelet activity [5], altered immune system with impaired wound healing [6] and increased postoperative breakdown of muscle protein [7,8]. However, from these data we cannot conclude that hypothermia *per se* is responsible for an adverse outcome.

Residual hypothermia at the end of surgery leads to shivering [9], increased circulating concentrations of plasma catecholamines, increased oxygen consumption and exaggerated haemodynamic responses [10]. These findings provide a possible mechanism for the hypothermia-related myocardial ischaemia reported in the period after major surgery [11].

A logical approach to unintentional hypothermia is to prevent it from occurring. This can be achieved to some extent by prewarming the patient's skin surface before induction of anaesthesia [12] or warming the inner and outer parts of the body throughout the course of anaesthesia and surgery [2, 8]. Most preventive methods aim to reduce the temperature gradient between patients and their immediate environment, thus minimizing heat loss via all routes (radiation, convection, conduction and evaporation) [13]. If these preventive measures are relatively unsuccessful in maintaining normothermia or are not easily instituted, the anaesthetist may use the alternative strategy of vigorously treating the residual heat debt by either pharmacological (opioids, vasodilators) or physiological (cutaneous warming) measures [14].

In a recent issue of the journal, Selldén, Bränström and Brundin [15] proposed a novel therapeutic approach to prevent perioperative hypothermia. They infused a mixture of amino acids i.v., before and during anaesthesia and surgery, with the aim of stimulating heat generation and whole body oxidative metabolism that otherwise would be depressed as a result of anaesthesia. The authors believed that such stimulation, started before anaesthesia and maintained during surgery, would counteract the perioperative loss of body heat and maintain the patient normothermic.

The thermic effect of feeding (also termed nutrient- or diet-induced thermogenesis) has been recognized for many years. It was thought originally that proteins had the major thermogenic effect, and indeed if nutrients are administered in isoenergetic amounts this is probably the case. Studies of the thermogenic effects of i.v. nutrients have shown that the response to a complete TPN mixture is only slightly larger than that to amino acids alone [16]. The normal diet contains only approximately 15% of the total energy content as protein, and when one considers the thermic effect of food ingested orally, carbohydrate is the major nutrient contributing to diet-induced thermogenesis. Indeed, ingestion of carbohydrate is sometimes accompanied by activation of facultative thermogenesis, an additional beta adrenoreceptor-mediated form of thermogenesis [17]. The amount of amino acids infused over 2 h by Selldén, Bränström and Brundin was equivalent to ingestion of 28 g of protein, that is approximately 50% of daily requirements. Thus some of the response observed was likely to be a result of an excessive rate of supply of amino acids, rather than a normally recruited physiological mechanism. This is even more likely given that the response observed in patients was much larger than that in healthy volunteers. It seems probable that preoperative medication, anaesthesia, or both, were responsible for this enhanced response to i.v. amino acids. It is interesting that infusion of amino acids at twice the rate used by Selldén, Bränström and Brundin increased resting energy expenditure (REE) by approximately 20% and that the effect was similar in healthy subjects and septic patients [18]. Thus the excessive thermogenic response to amino acids in the perioperative period appears to be restricted to that state, and does not interact with the metabolic disturbance accompanying sepsis. In the study of Selldén, Bränström and Brundin the increase in REE in patients was accompanied by an increase in body temperature. It seems unlikely that this increase in temperature was caused entirely by increased thermogenesis, and highly probable that there was also a reduction in heat loss compared with control subjects. Any decrease in body heat loss is likely to be achieved by a lower peripheral blood flow, presumably because of increased vascular tone. This effect, combined with the increased cardiorespiratory demands of amino acid-induced thermogenesis, would represent a considerable cardiovascular challenge to the patient in the perioperative period. This is likely to be tolerated well by healthy young patients, but could lead to problems in the elderly, or in those with impaired cardiorespiratory reserve. It would be valuable to determine the cardiorespiratory effect of an amino acid infusion during the perioperative period in patients of different ages.

Almost 50% of the thermogenesis caused by infusion of amino acids occurs in the splanchnic tissue. This represents the energy costs of protein synthesis, deamination and decarboxylation of amino acids, gluconeogenesis and urea synthesis. Although it is not clear which substrate is used mainly for these energy-requiring processes, it is speculated that amino acid oxidation contributes to a large extent.

Another remarkable finding of this study was the significant increase in oxidative metabolism in the amino acid infusion group at the end of anaesthesia and surgery, with values of 50–60% above baseline.

Administration of an amino acid mixture as a means of increasing REE and balancing the dissipation of body heat caused by anaesthesia and surgery over a period to time, poses several relevant questions; could the protective effect of perioperative hypothermia on body functions be disrupted by increased metabolic demand, increased splanchnic blood flow and cardiovascular workload? Second, could the combined effect of increased REE and sympathetic stimulation at the end of surgery and anaesthesia represent a major metabolic and cardiorespiratory load in compromised subjects with hepatic, renal or respiratory insufficiency?

A detailed evaluation of this method on the distribution of body heat in the anaesthetized patient and on the thermogenic interactions with different anaesthetic techniques is awaited. Similarly, the effect of infusion of amino acids on circulating concentrations of metabolites and hormones at the time of maximal stress may clarify the role of other substrates in the provision of energy.

The question remains as to whether or not the stress of hypothermia, as part of the overall injury response, should be prevented by further increasing REE or, in contrast, should measures be implemented to abolish or at least attenuate the sympathetic response associated with thermal and surgical stress. Large doses of i.v. opioids and regional block with local anaesthetics are valuable methods; however, the former method has several drawbacks in its application. In contrast, perioperative conduction block with local anaesthetics provides an excellent opportunity to attenuate significantly perioperative sympathetic stimulation, maintain cardiovascular stability, limit the postoperative increase in oxygen uptake and delay the rewarming phase [2,19].

The contention is not whether hypothermia should be prevented, but whether the stress associated with this disturbance is seen in the context of the injury response. Therefore, a rational approach would be aimed globally at modulating the production and loss of body heat, and the metabolic consequences.

F. CARLI
Department of Anaesthesia
McGill University, Royal Victoria Hospital
687 Pine Avenue West, Room F3.01
Montreal, Quebec, Canada H3A 1A1
I. A. MACDONALD
Department of Physiology and Pharmacology
Medical School, Queen's Medical Centre
Nottingham

References

1. Stoen R, Sessler DI. The thermoregulatory threshold is inversely proportional to isoflurane concentration. *Anesthesiology* 1990; **72**: 822–827.
2. Carli F, Webster J, Nandi P, Macdonald IA, Pearson J, Mehta R. Thermogenesis after surgery: effect of perioperative heat conservation and epidural anesthesia. *American Journal of Physiology* 1992; **263**: E441–E447.
3. Frank SR, Hoggins MS, Brescow MJ, Fleisher LA, Gorman RB, Sitzmann JV, Raff H, Beattie C. The catecholamine, cortisol and hemodynamic responses to mild perioperative hypothermia. *Anesthesiology* 1995; **82**: 83–93.
4. Heier T, Caldwell JE, Sessler DJ, Miller RD. Mild intraoperative hypothermia increases duration of action and spontaneous recovery of vecuronium blockade during nitrous oxide–isoflurane anaesthesia in humans. *Anesthesiology* 1991; **74**: 815–819.
5. Valeri C, Feingold H, Cassidy G, Ragno G, Khuri S, Altschule M. Hypothermia — induced reversible platelet dysfunction. *Annals of Surgery* 1987; **205**: 175–181.
6. Sheffield CW, Sessler DI, Hunt TK. Mild hypothermia during anesthesia decreases resistance to *Staphylococcus aureus* dermol infection. *Journal of Wound Healing and Regeneration* 1994; **2**: 48–56.
7. Carli F, Emery PW, Freemantle CAJ. Effect of perioperative normothermia on postoperative protein metabolism in elderly patients undergoing hip arthroplasty. *British Journal of Anaesthesia* 1989; **63**: 276–282.
8. Carli F, Webster J, Pearson M, Forrest J, Venkatesan D, Denham D, Halliday D. Postoperative protein metabolism: effect of nursing elderly patients for 24 h after abdominal surgery in a thermoneutral environment. *British Journal of Anaesthesia* 1991; **66**: 292–299.
9. Cohen M. An investigation into shivering following anaesthesia. Preliminary report. *Proceedings of the Royal Society of Medicine* 1967; **60**: 752–753.
10. Sessler DI, Rubinstein EH, Moayeri A. Physiological responses to mild perianesthetic hypothermia in humans. *Anesthesiology* 1991; **75**: 594–610.
11. Frank SM, Beattie C, Christopherson R, Norris EJ, Perier BA, Williams GM, Gottlieb SO. Unintentional hypothermia is associated with postoperative myocardial ischemia. *Anesthesiology* 1993; **78**: 468–476.
12. Just B, Trevien V, Delva E, Lienhart A. Prevention of intraoperative hypothermia by preoperative skin surface warming. *Anesthesiology* 1993; **79**: 214–218.
13. English MJM, Farmen C, Scott WAC. Heat loss in exposed volunteers. *Journal of Trauma* 1990; **30**: 422–425.
14. Sessler DI. Consequences and treatment of perioperative hypothermia. *Anesthesiology Clinics of North America* 1994; **12**: 425–456.
15. Selldén E, Bränström R, Brundin T. Preoperative infusion of amino acids prevents postoperative hypothermia. *British Journal of Anaesthesia* 1996; **76**: 227–234.
16. Arnold J, Leinhardt D, Carlson G, Gray P, Little RA, Irving MH. Thermogenic and hormonal responses to amino acid infusion in septic humans. *American Journal of Physiology* 1992; **263**: EI29–EI35.
17. Acheson K, Jequier E, Wahren J. Influence of beta blockade on glucose induced thermogenesis in man. *Journal of Clinical Investigation* 1983; **72**: 981–986.

18. Carlson GL, Gray P, Arnold J, Little RA, Irving MH. Thermogenic, hormonal and metabolic effects of a TPN mixture. Influences of glucose and amino acids. *American Journal of Physiology* 1994; **266**: E845–E851.
19. Carli F, Kulkarni P, Webster JD, Macdonald IA. Post-surgery epidural blockade with local anaesthetics attenuates the catecholamine and thermogenic response to perioperative hypothermia. *Acta Anaesthesiologica Scandinavica* 1995; **39**: 1041–1047.

British Journal of Anaesthesia 1996; **76**: 604–605

EDITORIAL II

Gastric tonometry to monitor tissue oxygenation: more than a gut feeling?

Monitoring tissue oxygenation has a vital role in anaesthesia and intensive care. Oxygenation of arterial blood is monitored clinically with arterial blood-gas analysis and pulse oximetry. Continuous measurement of Pa_{O_2} using an intra-arterial probe is being developed, but clinical use is limited. Pulse oximetry measures Sp_{O_2} in arterial capillaries. It does not account for carboxyhaemoglobin or haemoglobin and tends to overestimate Sp_{O_2} in severe hypoxaemia. While useful clinically to follow changes in arterial oxygenation, it is not equivalent to co-oximetry.

Whole body oxygen delivery (Do_2) is derived from the product of arterial oxygen content and cardiac output. This necessitates insertion of a pulmonary artery catheter to measure cardiac output by thermodilution, a method which has variations of 10–15% between measurements. Oxygen consumption ($\dot{V}o_2$) is the uptake of oxygen from arterial blood, and reflects oxygen consumed by cellular metabolism of the whole body. Direct measurement of $\dot{V}o_2$ using metabolic monitors is more accurate than calculation using the Fick principle (as the product of cardiac output and the arterial–mixed venous oxygen content difference). Modern metabolic monitors allow relatively easy and highly accurate and reproducible measurements. Low $\dot{V}o_2$ values indicate tissue hypoxia.

Recently, the concept of a pathological oxygen supply dependency has been debated. This proposes that patients with severe illness (e.g. sepsis and ARDS) have high *critical* Do_2 values. *Critical* Do_2 is Do_2 at which $\dot{V}o_2$ begins to decrease (i.e. when $\dot{V}o_2$ becomes dependent on Do_2), and has been demonstrated in experimental haemorrhage to be 8–9 ml kg^{-1} min^{-1}. Impaired oxygen extraction and utilization is an explanation for pathological oxygen supply dependency in critically ill patients. Thus high ("supranormal") values of Do_2 have been proposed as therapeutic end-points [1, 2]. Monitoring Do_2 and $\dot{V}o_2$ then assumes great importance; a significant increase in $\dot{V}o_2$ after measures to increase Do_2 would indicate that oxygenation was inadequate. However, outcome after use of "supranormal" therapy is not always better [3], and the concept of pathological oxygen supply dependency is not universally accepted [4].

Mixed venous oxygenation represents oxygen that is left after perfusion of the capillary beds in the systemic circulation, and indicates the balance between whole body oxygen transport and consumption. It can be monitored clinically as mixed venous oxygen saturation ($S\bar{v}_{O_2}$) either continuously using a fibreoptic pulmonary artery catheter, or intermittently by blood sampling. A low $S\bar{v}_{O_2}$ (< 65%) usually indicates tissue hypoxia, but normal values do not guarantee adequate oxygenation to all organs. Mixed venous blood represents blood only from perfused tissue, and maldistribution of microcirculatory flow underlies beds of tissue hypoxia in the face of an acceptable $S\bar{v}_{O_2}$.

Other than indices of oxygenation, blood lactate concentration is used clinically to assess tissue oxygenation. In the presence of hypoxia, anaerobic glycolysis metabolizes pyruvate to lactate. Ratios of pyruvate and lactate are probably better indices of the redox state than lactate alone. However, pyruvate measurements are not available routinely, whereas lactate concentrations can be measured promptly by modern lactate analysers. Serious tissue hypoxia is suggested by high blood lactate concentrations, but normal values are not always safe. High concentrations may also occur late in hypoxia, or may be associated with non hypoxic–ischaemic situations, such as when pyruvate substrate is increased by high metabolic rates (Pasteur effect) or inhibition of pyruvate dehydrogenase.

Apart from the inherent problems of measurement and accuracy with each of the above indices, they all reflect global whole body oxygenation. Normal or near-normal values mask poor blood flow and oxygenation to individual tissue capillary beds. The indices do not disclose or measure regional or organ hypoxia. Gastric tonometry, recently introduced to clinical practice, takes one step towards that goal. The principle is simple—inadequate regional perfusion results in anaerobic metabolism and gut intramucosal acidosis which is measured indirectly. A special tube with a carbon dioxide permeable silicone balloon at its tip is placed in the stomach. The balloon is filled with saline, and after 30–90 min equilibration, saline Pco_2 approaches mucosal Pco_2. Saline Pco_2 and actual arterial bicarbonate concentration (from a simultaneously collected arterial blood sample) are measured using a standard blood-gas analyser. Gastric pH (pH_i) is then calculated by applying a modified Henderson–Hasselbalch equation. Measurements can also be obtained with the tube inserted in the colon. H_2 receptor antagonists affect pH_i in healthy subjects but not in critically ill patients, and their routine use is unnecessary [5, 6]. The difference between arterial pH and pH_i ($pH_a - pH_i$ gradient) may be a more specific measure of gastric mucosal hypoxia.

Gastric tonometry is an attractive technique. It does not require intravascular placement, and splanchnic organs are particularly vulnerable to a failing circulation. Early response to detected gut ischaemia may prevent translocation of bacteria and endotoxin into the blood stream. Using gastric tonometry, gastric mucosal acidosis was reported to be common in critically ill patients [7,8], and was associated with increased complications and mortality in these patients and in those after major surgery [9,10] and trauma [11,12]. Unexpected splanchnic hypoxia was detected in cardiac patients after surgery [13–17], despite increased cardiac output and splanchnic blood flow after administration of dopexamine [16] and dobutamine [17]. The study by Welte and colleagues from Munich [18] found that pH_i decreased during orthotopic liver transplantation, although $D\mathrm{O}_2$ and haemodynamic variables remained unchanged.

Measurement of pH$_i$ is not without problems. Arterial bicarbonate is not a valid index of intracellular or extracellular bicarbonate in the gut, and its use to compute pH$_i$ is questioned [19]. Errors in calculated pH$_i$ can arise from analyses of saline $P\mathrm{CO}_2$ with different blood-gas analysers [20]. Cut-off values of pH$_i$ above which patients met with favourable outcome varied considerably in reported studies. The effects of inotropic agents (e.g. dopexamine) on pH$_i$ are conflicting [16,21]. The Munich group's finding that pH$_i$ was not a good predictor of graft viability [18] contrasted with that of a previous study [22]. Gastric tonometry assumes that gut intramucosal acidosis is invariably caused by hypoxia, but this may not be the case in sepsis [23]. Nevertheless, there are increasing data to suggest that low pH$_i$ values reflect inadequate perfusion of the gut. This splanchnic hypoperfusion is not indicated by haemodynamic or oxygen transport variables or illness severity scores (APACHE II and ISS) [12]. Although conventional measurements of metabolic acidosis may provide a similar clinical picture [24], pH$_i$ may be a more sensitive and earlier marker of hypoxia. We now have a new tool to monitor oxygenation. To validate its use, however, many questions still need to be answered, such as whether or not assessment of pH$_i$ changes in response to therapy or to guide therapy is useful, and what are acceptable pH$_i$ values?

T. E. Oh
Department of Anaesthesia and Intensive Care
Chinese University of Hong Kong
Prince of Wales Hospital
Shatin, New Territories
Hong Kong

References

1. Shoemaker WC, Appel PL, Kram HB. Hemodynamic and oxygen transport responses in survivors and nonsurvivors of high-risk surgery. *Critical Care Medicine* 1993; **21**: 977–990.
2. Tuschmidt J, Fired J, Astiz M, Rackow E. Elevation of cardiac output and oxygen delivery improves outcome in septic shock. *Chest* 1992; **102**: 216–220.
3. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *New England Journal of Medicine* 1994; **330**: 1717–1722.
4. Ronco JJ, Fenwick JC, Wiggs BR, Phang PT, Russell JA, Tweeddale MG. Oxygen consumption is independent of increases in oxygen delivery in septic patients who have normal or increased plasma lactate. *American Review of Respiratory Disease* 1993; **147**: 25–31.
5. Maynard N, Atkinson S, Mason R, Smithies M, Bihari D. Influence of intravenous ranitidine on gastric intramucosal pH in critically ill patients. *Critical Care Medicine* 1994; **22**, A79.
6. Baigorri F, Calvert X, Duarte M, Saura P, Jubert P, Royo C, Joseph D, Artigas A. Effect of ranitidine treatment in gastric intramucosal pH determinations in critically ill patients. *Intensive Care Medicine* 1994; **20** (Suppl. 2): S2.
7. Maynard N, Bihari D, Beale R, Smithies M, Baldock G, Mason R, McColl I. Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure. *Journal of the American Medical Association* 1993; **270**: 1203–1210.
8. Marik PE. Gastric intramucosal pH. A better predictor of multiorgan dysfunction syndrome and death than oxygen-derived variables in patients with sepsis. *Chest* 1993; **104**: 225–229.
9. Mythen MG, Webb AR. Intra-operative gut mucosal hypoperfusion is associated with increased post-operative complications and cost. *Intensive Care Medicine* 1994; **20**: 99–104.
10. Bjorck M, Hedberg B. Early detection of major complications after abdominal aortic surgery: predictive value of sigmoid colon and gastric intramucosal pH monitoring. *British Journal of Surgery* 1994; **81**: 25–30.
11. Chang MC, Cheatham ML, Nelson LD, Rutherford EJ, Morris JA jr. Gastric tonometry supplements information provided by systemic indicators of oxygen transport. *Journal of Trauma* 1994; **37**: 488–494.
12. Roumen RM, Vreugde JP, Goris RJ. Gastric tonometry in multiple trauma patients. *Journal of Trauma* 1994; **36**: 313–316.
13. Ohri SK, Bowles CT, Siddiqui A, Khaghani A, Keogh BE, Wright G, Yacoub MH, Taylor KM. The effect of cardiopulmonary bypass on gastric and colonic mucosal perfusion: a tonometric assessment. *Perfusion* 1994; **9**: 101–108.
14. Gaer JA, Shaw AD, Wild R, Swift RI, Munsch CM, Smith PL, Taylor KM. Effect of cardiopulmonary bypass on gastrointestinal perfusion and function. *Annals of Thoracic Surgery* 1994; **57**: 371–375.
15. Niinikoski J, Kuttila K. Adequacy of tissue oxygenation in cardiac surgery: regional measurements. *Critical Care Medicine* 1993; **21**: 77–83.
16. Uusaro A, Ruokinen E, Takala J. Gastric mucosal pH does not reflect changes in splanchnic blood flow after cardiac surgery. *British Journal of Anaesthesia* 1995; **74**: 140–154.
17. Parviainen I, Ruokonen E, Takala J. Dobutamine-induced dissociation between changes in splanchnic blood flow and gastric intramucosal pH after cardiac surgery. *British Journal of Anaesthesia* 1995; **74**: 277–282.
18. Welte M, Pichler B, Groh J, Anthuber M, Jauch K-W, Pratschke E, Lenhart F-P, Haller M, Frey L, Peter K. Perioperative mucosal pH and splanchnic endotoxin concentration in orthotopic liver transplantation. *British Journal of Anaesthesia* 1996; **76**: 90–98.
19. Groeneveld AB, Kolkman JJ. Splanchnic tonometry: a review of physiology, methodology, and clinical applications. *Journal of Critical Care* 1994; **9**: 198–210.
20. Takala J, Parviainen I, Siloaho M, Ruokonen E, Hamalainen E. Saline $P\mathrm{CO}_2$ is an important source of error in the assessment of gastric intramucosal pH. *Critial Care Medicine* 1994; **22**: 1877–1879.
21. Smithies M, Yee TH, Jackson L, Beale R, Bihari D. Protecting the gut and the liver in the critically ill: effects of dopexamine. *Critical Care Medicine* 1994; **22**: 789–795.
22. Frenette L, Doblar RG, Singer D, Cox J, Ronderos J, Poplawski S, Ranjan D. Gastric intramural pH as indicator of early allograft viability in orthotopic liver transplantation. *Transplantation* 1994; **58**: 292–297.
23. Hotchkiss RS. Reevaluation of the role of cellular hypoxia and bioenergetic failure in sepsis. *Journal of the American Medical Association* 1992; **267**: 1503–1510.
24. Boyd O, Mackay CJ, Lamb G, Bland JM, Grounds RM, Bennett ED. Comparison of clinical information gained from routine blood-gas analysis and from gastric tonometry for intramural pH. *Lancet* 1993; **341**: 142–146.

British Journal of Anaesthesia 1996; **76**: 606–610

CLINICAL INVESTIGATIONS

Continuous extradural infusion of ropivacaine for prevention of postoperative pain after major orthopaedic surgery

G. Turner, D. Blake, M. Buckland, D. Chamley, P. Dawson, C. Goodchild, J. Mezzatesta, D. Scott, A. Sultana, S. Walker, M. Hendrata, P. Mooney and M. Armstrong

Summary

We studied 151 patients undergoing total hip or knee arthroplasty, or cruciate ligament reconstruction in a multicentre study in Australia and New Zealand. Patients were openly allocated randomly to one of five treatment groups or to a control group. General anaesthesia was induced after introduction of extradural block with 0.5% ropivacaine. After surgery, patients received an extradural infusion of 0.2% ropivacaine at 6, 8, 10, 12 or 14 ml h^{-1} or received no postoperative extradural infusion (control group). All patients had access to i.v. PCA morphine for supplementary analgesia. Morphine consumption was lower in all treatment groups compared with the control group, decreasing with increasing ropivacaine infusion rate. Median VAS scores were lower in all ropivacaine infusion groups compared with the control group for the first 10 h of the study; however by the end of the study, VAS scores were similar in all groups. The higher ropivacaine infusion rates caused a slower convergence of spread of the initial sensory block and a higher degree of motor block. The overall incidence of side effects was similar, with the exception of a higher incidence of urinary retention and hypotension in the groups receiving the higher rates of ropivacaine. The quality of treatment scores were similar for all treatment groups (*Br. J. Anaesth.* 1996; **76**: 606–610)

Key words

Anaesthetics local, ropivacaine. Anaesthetic techniques, extradural. Analgesia, postoperative. Pain, postoperative. Surgery, orthopaedic.

Ropivacaine is a new long-acting anaesthetic, belonging to the same homologous series of compounds as bupivacaine and mepivacaine. It is the first enantiomerically pure local anaesthetic and exists as the S-enantiomer. Ropivacaine has pharmacodynamic and pharmacokinetic properties resembling those of bupivacaine in animals [1–3] and humans [4–6]. However, ropivacaine has a lower potential for central nervous system and cardiovascular toxic side effects than bupivacaine in animals [7]. In preclinical studies, ropivacaine produced less central nervous system and cardiotoxicity than bupivacaine [8]. Furthermore, in human volunteers, ropivacaine has also been shown to be less prone than bupivacaine to produce central nervous system and cardiovascular changes after i.v. infusion [9].

In double-blind comparative studies of extradural anaesthesia, ropivacaine has shown overall clinical efficacy and tolerability similar to that of bupivacaine [10–12]. Similarly, ropivacaine has proved efficacious in producing postoperative analgesia after lower and upper abdominal surgery [13]. Studies in healthy volunteers and postoperative patients have found 0.2% ropivacaine to be the optimal concentration for infusion [13, 14].

In this study we investigated the volume response relationship of extradural infusion of 0.2% ropivacaine for analgesia.

Patient and methods

After obtaining Institutional Ethics Committee approval and written informed consent, we studied 151 patients in six institutions. All patients were ASA I–III, aged 24–75 yr and undergoing total hip or knee arthroplasty, or cruciate ligament reconstruction. Patients were premedicated with a benzodiazepine before insertion of an extradural catheter in the L1–5 interspaces. A test dose of 1.5% lignocaine 4 ml with adrenaline 5 μg ml^{-1} was used. After confirming satisfactory placement of the catheter, 0.5% ropivacaine 5–20 ml was injected over a 5-min period. Another 5 ml of 0.5% ropivacaine were injected if surgical anaesthesia was not achieved to T10, 30 min after the main dose. When adequate local anaesthesia was obtained, general anaesthesia

---

G. Turner*, MB, BS, FRCA, FANZCA, M. Armstrong, RN, Royal Perth Hospital, Perth, WA, Australia. D. Blake, BMEDSCI, MB, BS, PHD, FANZCA, P. Dawson, MB, BS, FANZCA, Royal Melbourne Hospital, Melbourne, Vic, Australia. M. Buckland, MB, BS, FANZCA, A. Sultana, MD, MRCP, FANZCA, M. Hendrata, RN, Alfred Hospital, Melbourne, Vic, Australia. D. Chamley, BSC, MB, CHB, FANZCA, S. Walker, BSC, MB, CHB, FANZCA, Middlemore Hospital, Auckland, New Zealand. C. Goodchild, MA, MB, BCHIR, PHD, FRCA, J. Mezzatesta, MB, BS, FANZCA, Monash Medical Centre, Melbourne, Vic, Australia. D. Scott, MB, BS, FANZCA, P. Mooney, RN, St Vincent's Hospital, Melbourne, Vic, Australia. Accepted for publication: January 4, 1996.

*Address for correspondence: Department of Anaesthesia, Royal Perth Hospital, Box S1400 GPO, Perth, WA 6001, Australia.

was induced with thiopentone or propofol i.v. Neuromuscular block was produced with either atracurium, vecuronium, pancuronium or suxamethonium. Anaesthesia was maintained with a volatile agent and nitrous oxide in oxygen. Up to 250 μg of fentanyl were administered i.v. during the procedure at the anaesthetist's discretion. During surgery, top-up doses of 0.5% ropivacaine 3–5 ml were given extradurally at 30-min intervals if required. Patients were allocated randomly to a control group or to receive an extradural infusion of 0.2% ropivacaine at one of the following rates: 6, 8, 10, 12 or 14 ml h^{-1}. The control group did not receive any postoperative extradural infusion. All patients had access to i.v. morphine or pethidine delivered by a patient-controlled analgesia (PCA) system. If for any reason patients did not tolerate morphine, PCA was continued with pethidine; pethidine 10 mg was equivalent to morphine 1 mg. The PCA was set to give a bolus dose of morphine 1 mg or pethidine 10 mg with a 5-min lockout period, and no 4 h dose limit.

The extent of motor and sensory block were determined before commencement of surgery. Motor weakness was determined according to a modified Bromage scale (0 = no motor block, 1 = inability to raise extended legs, 2 = inability to flex knees, 3 = inability to flex ankle joints). In cases of asymmetric block the highest (numerical) value was recorded. Sensory analgesia was determined as loss of sensation using a 27-gauge short Bayer dental needle. The amount of supplementary morphine or pethidine delivered by PCA, extent of sensory and motor weakness (Bromage scale) and pain scores at rest (on a 100-mm visual analogue scale) were recorded for 21 h after operation at three times: 0–4 h, 4–8 h and 8–21 h. After this time ropivacaine infusion was stopped. At the end of the 21-h infusion, patients were asked to rate the overall quality of their treatment on a four-point scale (1 = poor, 2 = fair, 3 = good, 4 = excellent).

Patient data were analysed using *t* and chi-square tests. Morphine consumption, VAS scores, sensory spread, motor block and quality of treatment were analysed with stratified Wilcoxon rank sum tests controlling for institution. Differences referred to as statistically significant corresponded to a two-sided *P* value less than 0.01.

Results

Of the 151 patients recruited into the study, 128 were valid for efficacy data analysis. Sixteen patients were excluded because they did not receive postoperative treatment according to the study procedure after enrolment. Of these an extradural catheter could not be sited satisfactorily in six patients, there was inadvertent subdural, subarachnoid or i.v. placement in five patients, there was inadequate spread of sensory block before surgery in two patients and no block at the end of surgery in one patient. Surgery was cancelled after extradural block was established on one occasion and surgery extended beyond 4 h on another occasion. Seven patients were excluded because of further study violations: two patients had catheter displacement causing leakage of the extradural infusion or loss of sensory block, three patients had the infusion turned off or the rate changed outside of study guidelines, one patient developed subarachnoid block from presumed catheter migration and one patient had an inadequate block before surgery. Patient data are shown in table 1. There were no significant differences between the groups. Two patients in the control group received pethidine instead of morphine via PCA and four, one, three, two and four patients in the 6-, 8-, 10-, 12- and 14-ml h^{-1} groups, respectively.

Total morphine consumption for all six groups is shown in figure 1 in addition to the amount consumed in the first 4 h after operation, 4–8 h and 8–21 h. Median total morphine consumption during the study was 36 mg in the control group, 13 mg in the 6-ml h^{-1} group, 26 mg in the 8-ml h^{-1} group, 12 mg in the 10-ml h^{-1} group, 11 mg in the 12-ml h^{-1} group and 3 mg in the 14-ml h^{-1} group. There was a trend towards a dose–response relationship with decreasing morphine requirements in groups receiving the higher extradural ropivacaine infusion rates. At each time morphine consumption was greatest in the control group, which was statistically significant compared with the other groups, except for the 8-ml h^{-1} group at all times and the 10-ml h^{-1} group at 8–21 h. Morphine consumption in patients who received ropivacaine 14 ml h^{-1} was significantly lower than the control, 6- and 8-ml h^{-1} groups at all times. Table 2 shows the *P* values for comparison of total morphine consumption over the 21-h period between the control and ropivacaine groups.

Median VAS scores in the control group were 18–30 for the first 10 h whereas VAS scores for the ropivacaine groups did not exceed 8 during the same period (fig. 2). At 10–21 h the difference in VAS scores between the groups was small, mainly because of a decrease in VAS scores in the control group. At 4 h, VAS scores were significantly lower in the ropivacaine groups compared with the control group, with the exception of patients who received the lowest ropivacaine infusion rate (6 ml h^{-1}). At 8 h, VAS scores were still significantly lower in the 10-, 12- and 14-ml h^{-1} groups compared with the control group and lower in the 12- and 14-ml h^{-1} groups compared with the 8-ml h^{-1} group. At 21 h the only significant difference in VAS scores was between the 14- and 8-ml h^{-1} groups.

The median upper limit of sensory block in the ropivacaine groups was different at 2 h after the start of the infusion (fig. 3): T10 in the 6- and 8-ml h^{-1} groups; T9 in the 10- and 14-ml h^{-1} groups; and T8 in the 12-ml h^{-1} group. These levels had receded by the end of the infusion to L2 in the 6-ml h^{-1} group; L1 in the 8- and 12-ml h^{-1} groups; and T12 in the 10- and the 14-ml h^{-1} groups. The lower limit of sensory block was S2–S1 in all groups 2 h after the start of extradural infusion but had receded by the end of the infusion, 21 h after operation to: L4–L3 in the 6-ml h^{-1} group; L4 in the 8-ml h^{-1} group; L5 in the 10- and 12-ml h^{-1} groups; and S1–L5 in the 14-ml h^{-1} group. The median upper and lower limits of sensory block in the control group were L1 and L5,

Table 1 Patient data (mean (SD or range) or number). * One value missing from the fentanyl doses in the 14-ml h^{-1} group

	Control	Ropivacaine group				
		6 ml h^{-1}	8 ml h^{-1}	10 ml h^{-1}	12 ml h^{-1}	14 ml h^{-1}
	(n = 20)	(n = 22)	(n = 23)	(n = 23)	(n = 24)	(n = 23)
Age (yr)	58.4 (26–75)	58.1 (24–75)	61.2 (25–73)	56.4 (26–73)	64.6 (33–75)	61.5 (24–75)
Weight (kg)	74.5 (15.4)	77.5 (10.2)	78.2 (14.3)	77.7 (13.4)	76.7 (11.6)	72.4 (14.8)
Sex (M/F)	10/10	7/15	12/11	10/13	14/10	11/12
Operation (n)						
Hip	12	14	12	16	18	12
Knee	5	5	7	5	6	6
Cruciate ligament	3	3	4	2	0	5
ASA I/II/III	5/12/3	6/14/2	6/15/2	5/16/2	1/21/2	2/20/1
Fentanyl (μg)						*
0	10	7	6	9	11	7
50–100	6	7	10	3	7	11
101–200	3	6	7	10	6	4
201–300	1	2	0	1	0	0

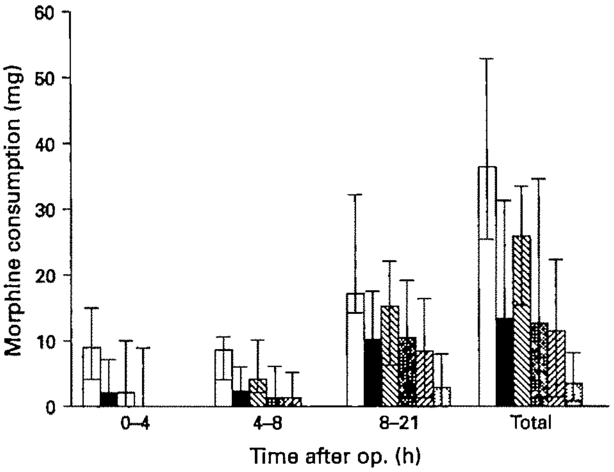


Figure 1 Median (interquartile range) morphine consumption for each ropivacaine infusion group: 6 ml h^{-1} (n = 20) (■), 8 ml h^{-1} (n = 21) (▧), 10 ml h^{-1} (n = 21) (▦), 12 ml h^{-1} (n = 22) (▨), 14 ml h^{-1} (n = 20) (▩). □ = Control (n = 17).

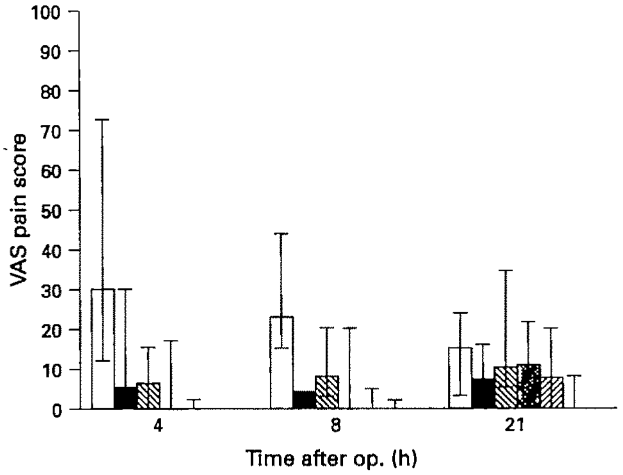


Figure 2 Median (interquartile range) VAS pain scores for each ropivacaine infusion group: 6 ml h^{-1} (n = 21) (■), 8 ml h^{-1} (n = 21) (▧), 10 ml h^{-1} (n = 21) (▦), 12 ml h^{-1} (n = 22) (▨), 14 ml h^{-1} (n = 22) (▩). □ = Control (n = 17).

Table 2 Significant differences in total morphine consumption between the ropivacaine (R) and control groups over the 21-h study

Comparison	P
Control *vs* R 6 ml h^{-1}	0.002
Control *vs* R 8 ml h^{-1}	0.126
Control *vs* R 10 ml h^{-1}	0.002
Control *vs* R 12 ml h^{-1}	0.000
Control *vs* R 14 ml h^{-1}	0.000

respectively, 2 h after the start of the infusion, and sensory block had resolved completely 6 h after operation.

The number of patients exhibiting significant motor block with muscle weakness and the severity of this effect diminished with time after operation, even during the 0.2 % ropivacaine infusions. This occurred in all ropivacaine groups (table 3). After 4 h there was no motor block in the control group yet

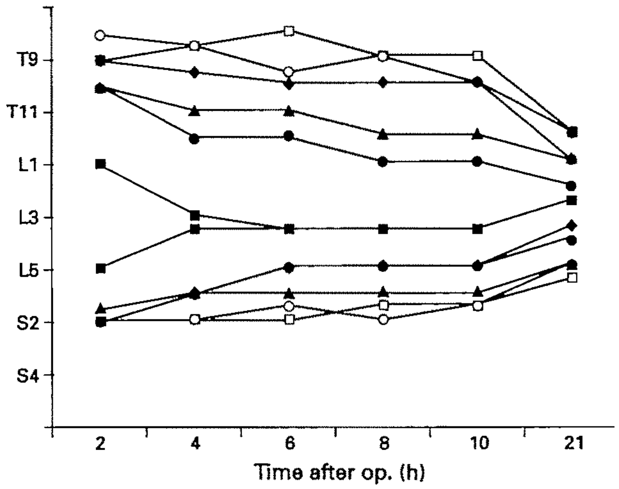


Figure 3 Median upper and lower limit of sensory block for each ropivacaine infusion rate during the study period: ● = 6 ml h^{-1}, ▲ = 8 ml h^{-1}, ◆ = 10 ml h^{-1}, ○ = 12 ml h^{-1}., □ = 14 ml h^{-1}. ■ = Control.

Table 3 Motor block at each time for each treatment group (%)

		Ropivacaine group				
Bromage score	Control ($n = 19$)	6 ml h^{-1} ($n = 21$)	8 ml h^{-1} ($n = 21$)	10 ml h^{-1} ($n = 22$)	12 ml h^{-1} ($n = 22$)	14 ml h^{-1} ($n = 22$)
At 4 h						
0	100	57	62	36	23	32
1	0	38	38	46	45	32
2	0	5	0	9	14	27
3	0	0	0	9	18	9
At 8 h						
0	100	71	71	50	41	32
1	0	29	29	36	32	36
2	0	0	0	9	14	32
3	0	0	0	5	13	0
At 21 h						
0	100	81	86	86	55	50
1	0	19	9	14	40	23
2	0	0	5	0	0	27
3	0	0	0	0	5	0

Table 4 Quality of treatment scores (%)

		Ropivacaine group				
	Control ($n = 17$)	6 ml h^{-1} ($n = 20$)	8 ml h^{-1} ($n = 20$)	10 ml h^{-1} ($n = 20$)	12 ml h^{-1} ($n = 22$)	14 ml h^{-1} ($n = 18$)
4 Excellent	59	80	65	75	68	61
4 Good	29	10	20	15	18	39
2 Fair	12	5	10	5	9	0
1 Poor	0	5	5	5	5	0

Table 5 Incidence of side effects in each treatment group during the 21-h postoperative period (%)

		Ropivacaine				
	Control ($n = 20$)	6 ml h^{-1} ($n = 22$)	8 ml h^{-1} ($n = 23$)	10 ml h^{-1} ($n = 23$)	12 ml h^{-1} ($n = 24$)	14 ml h^{-1} ($n = 23$)
Nausea	50	50	48	48	58	61
Vomiting	20	27	13	26	13	17
Hypotension	10	14	17	13	13	43
Urinary retention	0	9	4	9	21	30

there was weakness of Bromage scale 2 or more in 5%, 18%, 32% and 36% of patients in the 6-, 10-, 12- and 14-ml h^{-1} groups, respectively. There was a statistically significant difference in motor block 4 h after operation between the control and all ropivacaine groups, between the 12-ml h^{-1} group and the 6- and 8-ml h^{-1} groups and between the 8- and 14-ml h^{-1} groups. At 8 h after operation there was still a statistically significant difference between the control and the 10-, 12- and 14-ml h^{-1} groups, between the 14-ml h^{-1} group and the 6- and 8-ml h^{-1} groups and also between the 8- and 12-ml h^{-1} groups. There was no block in the 6- or 8-ml h^{-1} groups, however motor weakness was Bromage scale 2 or more in 14%, 27% and 32% of patients in the 10-, 12- and 14-ml h^{-1} groups, respectively. After 20 h there was a statistically significant difference between the control and 12- and 14-ml h^{-1} groups and between the 14-ml h^{-1} and the 10- and 12-ml h^{-1} groups. At this time there were still 5% of the 8- and 12-ml h^{-1} groups and 27% of the 14-ml h^{-1} group with Bromage motor weakness of 2 or more.

There was no statistically significant difference between any of the treatment groups with respect to quality of treatment scores (table 4).

Table 5 shows the incidence of the most frequent side effects in the 21-h postoperative infusion period. The incidence of nausea and vomiting was similar for all treatment groups. More patients experienced urinary retention in the groups receiving higher infusion rates of ropivacaine, and hypotension (systolic arterial pressure ≤ 80 mm Hg or a decrease in arterial pressure requiring drug treatment) was more prevalent in the 14-ml h^{-1} group than in the other groups.

Discussion

We found that postoperative pain relief was better with extradural infusion of 0.2% ropivacaine combined with PCA morphine than with PCA morphine alone. PCA morphine is a common postoperative analgesia technique and is used frequently as a rescue medication in analgesia studies. Patients receiving extradural ropivacaine required less supplementary morphine from PCA and achieved lower pain scores than the control groups. There was a trend to a volume response relationship, the higher extradural ropivacaine infusion rates requiring less supplementary PCA morphine; 14 ml h^{-1} was significantly different from the control, 6-ml h^{-1} and 8-ml h^{-1} groups at all times.

VAS scores in the ropivacaine groups were acceptably low, although they were assessed only at rest. However, VAS scores in the morphine PCA group were higher at 4 and 6 h after operation before decreasing to lower levels.

The incidence of motor block was low, but more marked in the 12- and 14-ml h^{-1} infusion groups. The frequency and intensity of motor block decreased throughout the 21-h period. By 21 h, however, there were still 5% and 27% of patients, respectively, with a Bromage score of 2 or more in the 12- and 14-ml h^{-1} groups. Although the incidence of hypotension was similar in all groups, with the exception of the 14-ml h^{-1} group, there were more episodes of urinary retention in the 12- and 14-ml h^{-1} groups. This combined with the higher incidence of motor block at these infusion rates may increase the need for urinary catheterization and delay early postoperative mobilization. Infusion rates greater than 8 ml h^{-1} caused sensory block in all lumbar segments. This is in accordance with results of Zaric and colleagues [14] who found that an infusion of 0.2% ropivacaine 10 ml h^{-1} gave a sensory block of nine dermatomes decreasing to five dermatomes after 21 h. In this study, sensory block in the 10-ml h^{-1} group decreased from 10 to five dermatomes over the 21-h period.

In general, all infusion rates of ropivacaine gave satisfactory analgesia when used together with PCA morphine. However, the higher infusion rates of 12 and 14 ml h^{-1} caused increased incidences of motor block and urinary retention without providing significantly improved analgesia compared with the 10-ml h^{-1} group, while the 6-ml h^{-1} group failed to block all lumbar segments.

Acknowledgement

We thank Astra Pharmaceuticals who funded this study.

References

1. Akerman B, Hellberg I, Trossvik C. Primary evaluation of the local anaesthetic properties of the aminuteso agent ropivacaine (LEA 103). *Acta Anaesthesiologica Scandinavica* 1988; **32**: 571–578.
2. Feldman HS, Covino BG. Comparative motor blocking effects of bupivacaine and ropivacaine, a new amide local anesthetic in the rat and dog. *Anesthesia and Analgesia* 1988; **67**: 1047–1052.
3. Arthur G, Feldman H, Covino BG. Comparative pharmacokinetics of bupivacaine and ropivacaine, a new amide local anesthetic. *Anesthesia and Analgesia* 1988; **67**: 1053–1058.
4. Katz JA, Bridenbaugh PO, Knarr DC, Helton SH, Denson DD. Pharmacokinetics of bupivacaine and ropivacaine, a new amide local anesthetic. *Anesthesia and Analgesia* 1988; **70**: 16–21.
5. Concepcion M, Arthur RG, Steele SM, Bader AM, Covino BG. A new local anesthetic, ropivacaine. Its epidural effects in humans. *Anesthesia and Analgesia* 1990; **70**: 80–85.
6. Whitehead E, Arrigoni B, Bannister J. An open study in extradural anaesthesia. *British Journal of Anaesthesia* 1990; **64**: 67–71.
7. Rutten AJ, Nancarrow C, Mather LE, Isley AH, Runciman WB, Upton RN. Hemodynamic and central nervous system effects of lidocaine, bupivacaine and ropivacaine in sheep. *Anesthesia and Analgesia* 1989; **69**: 291–299.
8. Feldman HS. Toxicity of local anaesthetic agents. In: Rice SA, Fish KJ, eds. *Anaesthetic Toxicity*. New York: Raven Press, 1994; 7: 107–133.
9. Scott DB, Lee A, Fagan D, Bowler GMR, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesthesia and Analgesia* 1989; **69**: 563–569.
10. Kerkkamp HEM, Gielen MJM, Edstrom HH. Comparison of 0.75% ropivacaine with epinephrine and 0.75% bupivacaine with epinephrine in lumbar epidural anesthesia. *Regional Anesthesia* 1990; **15**: 204–207.
11. Brockway MS, Bannister J, McClure JH, McKeown D, Wildsmith JAW. Comparison of extradural ropivacaine and bupivacaine. *British Journal of Anaesthesia* 1991; **66**: 31–37.
12. Brown DL, Carpenter RL, Thompson GE. Comparison of 0.5% ropivacaine and 0.5% bupivacaine for epidural anesthesia in patients undergoing lower-extremity surgery. *Anesthesiology* 1990; 72: 633–636.
13. Scott DA, Chamley D, Mooney PH, Mark T, Deam RK. Epidural ropivacaine infusion for post operative analgesia following major abdominal surgery—a dose finding study. *Anesthesiology* 1994; **81**: S3A, A970.
14. Zaric D, Axelsson K, Nydahl PA, Philipsson L, Samuelsson L. Sensory and motor blockade during continuous epidural infusion of ropivacaine 0.1%, 0.2% and 0.3% in volunteers—a double-blind study. *Regional Anesthesia* 1994; **19** (Suppl. 2S): 60.

British Journal of Anaesthesia 1996; **76**: 611–615

Patient-controlled extradural analgesia with bupivacaine, fentanyl, or a mixture of both, after Caesarean section

D. W. COOPER, D. M. RYALL, F. E. MCHARDY, S. L. LINDSAY AND S. S. ELDABE

Summary

In this randomized, double-blind study of 60 patients, we have assessed the analgesic efficacy of extradural bupivacaine and extradural fentanyl, either alone or in combination, after Caesarean section. Patients received 0.1% bupivacaine (group B), fentanyl 4 μg ml^{-1} (group F) or 0.05% bupivacaine combined with fentanyl 2 μg ml^{-1} (group BF) by patient-controlled extradural analgesia (PCEA). Adding fentanyl to bupivacaine reduced the dose of bupivacaine by up to 68%, improved analgesia at rest and decreased PCEA use. Motor and sensory block were decreased, but there was more pruritus. Overall patient satisfaction was increased. Adding bupivacaine to fentanyl reduced the dose of fentanyl by up to 57% without altering pain scores or PCEA use. Sensory block increased but pruritus did not decrease. Bupivacaine 0.05% produced clinically significant leg weakness in three patients. Overall patient satisfaction was not altered. There was a significant additive analgesic effect between 0.05% bupivacaine and fentanyl but no clinical benefit was demonstrated from using the combination compared with fentanyl alone for this group of postoperative patients. (*Br. J. Anaesth.* 1996; **76**: 611–615)

Key words

Anaesthetic techniques, extradural. Analgesics opioid, fentanyl. Anaesthetics local, bupivacaine. Analgesia, patient-controlled. Anaesthesia, obstetric.

Extradural fentanyl produces effective postoperative analgesia with a low incidence of serious side effects. Extradural bupivacaine can produce excellent analgesia at the expense of dose-dependent side effects from sensory, motor and sympathetic block. Laboratory work has demonstrated a supra-additive analgesic effect between intrathecal local anaesthetics and opioids [1]. Despite this finding it is unclear if it is clinically beneficial to add bupivacaine to fentanyl for postoperative extradural analgesia. Some studies have shown no benefits from this practice [2–5], whereas others have demonstrated either reductions in fentanyl dose, improved analgesia, or both [6–10].

The aims of this study were to assess the effects of combining extradural bupivacaine with extradural fentanyl and to compare the two drugs for analgesia after Caesarean section. Half strength solutions were used for the combination group. This, in conjunction with patient-controlled extradural analgesia (PCEA), was to try to minimize the dose of each drug used in combination, while at the same time maintaining analgesic efficacy. Analgesic dose requirements, visual analogue pain scores, PCEA use, side effects and overall patient satisfaction were examined over the first 24 h after operation.

Patients and methods

The study was double-blind and approved by the local Hospital Ethics Committee. After obtaining informed consent, we studied 60 ASA I–II patients undergoing morning elective Caesarean section under extradural analgesia.

In the anaesthetic room, before insertion of the extradural catheter, baseline arterial pressure, heart rate and ventilatory frequency were recorded with the patient lying in the left lateral position. In all patients an extradural catheter was inserted at L2–3 or an adjacent space. Neural block was produced using 0.5% bupivacaine. After an initial 3-ml test dose the subsequent 10 ml contained fentanyl 50 μg. Thereafter sufficient bupivacaine was administered to achieve a block to T4–T6. Further intraoperative analgesia, if required, was provided by i.v. fentanyl or alfentanil.

From the end of operation patients were free to use a PCEA device which was allocated randomly to deliver either 0.1% bupivacaine (group B), fentanyl 4 μg ml^{-1} (group F) or 0.05% bupivacaine combined with fentanyl 2 μg ml^{-1} (group BF). The PCEA device was programmed to allow a 5-ml bolus with a 10-min lockout interval. Patient grouping was decided by opening a blank envelope from a set of 60 shuffled envelopes containing either the code for group B ($n = 20$), F ($n = 20$) or BF ($n = 20$). The investigator who set up the PCEA was not involved with subsequent patient management or assessment. Patients, nursing and medical staff were unaware of patient grouping.

The study lasted for 24 h from the end of operation. Patients were kept in a recovery area for 4 h and then transferred to the postnatal ward. Postoperative analgesia was provided solely by PCEA. All patients were educated in the use of PCEA and informed that they had to wait for 10 min

---

DAVID W. COOPER, MB, BS, FRCA, DAVID M. RYALL, MB, CHB, FRCA, FIONA E. MCHARDY, MB, CHB, SUSAN L. LINDSAY, MB, BS, FRCA, SAMEH S. ELDABE, MB, CHB, FRCA, Department of Anaesthetics, South Cleveland Hospital, Middlesbrough, Cleveland TS4 3BW.
Accepted for publication: December 12, 1995.

before the next dose would be available. If analgesia was judged to be inadequate by the patient herself, nursing or medical staff, then the study was stopped at that point. The extradural catheter was left in position for assessment by an anaesthetist and the patient was given alternative analgesia. Data were analysed provided the catheter had not become displaced.

Volumes of analgesic solution self-administered were recorded at 0.5, 4, 8, 12 and 24 h. At the same times visual analogue scores for pain (VAS) at rest and on coughing (100-mm scale; 0 = no pain, 100 mm = worst pain imaginable), and also sedation scores were recorded. The presence or absence of nausea, vomiting and pruritus was recorded for the time periods 0–0.5, 0.5–4, 4–8, 8–12 and 12–24 h. Pruritus was graded as mild, moderate or severe. A verbal rating score (VRS) for overall satisfaction (0 = excellent, 1 = adequate, 2 = fair, 3 = poor) was recorded for those patients completing 24 h. VRS = 3 if the patient stopped early because of side effects or inadequate analgesia, despite good catheter position. Arterial pressure and ventilatory frequency were measured every 1–2 h and more frequently if systolic arterial pressure (AP) was less than 100 mm Hg or ventilatory frequency less than 10 bpm.

Between 20 and 24 h, patients were assessed on one occasion by an anaesthetist for maximum sensory block, motor block, postural hypotension (supine, sitting and standing AP using an automated NIBP device) and ability to walk unaided. Maximum sensory block to ethyl chloride spray was assessed on a four-point scale: 0 = no area of reduced sensation, 1 = area of reduced sensation but still cold, 2 = area of reduced sensation but not cold and 3 = area of complete absence of sensation. Motor block was assessed on a four-point scale: 0 = no weakness detected, 1 = able to straight leg raise, but power reduced, 2 = unable to straight leg raise and 3 = unable to raise knee off bed. Ability to walk was assessed only if there was no leg weakness or postural hypotension and the patient felt sufficiently pain free.

A computer package (SPSS) was used for statistical analysis. Results were compared using Mann–Whitney and Kruskal–Wallis tests, with $P < 0.05$ taken as significant.

Results

We studied 60 patients, 20 in each group. Four patients (two in group B, one in group F and one in group BF) were subsequently excluded because the extradural catheter became dislodged in the postoperative period. Groups were matched for age, height, weight and operative analgesia (table 1).

Eight additional patients (seven in group B, one in group F) stopped before completing 24 h. Five stopped in group B because of inadequate analgesia despite good catheter position (one at 4–8 h and four at 12–24 h), compared with none in groups F or BF. Another two patients in group B stopped at 12–24 h because they did not like the feeling of numbness in their legs. One patient in group F stopped at 12–24 h because of a malfunction in the PCEA device. Data from these patients were included up to the assessment time before premature cessation of the study.

Table 1 Patient data for groups B, F and BF (mean (range or SD))

	Group B	Group F	Group BF
n	18	19	19
Age (yr)	28 (19–41)	29 (20–42)	31 (20–44)
Height (cm)	161 (9)	159 (7)	161 (7)
Weight (kg)	77 (8)	78 (16)	74 (12)
Operative drugs			
Bupivacaine 0.5% (ml)	25 (6)	25 (5)	24 (4)
Fentanyl (μg)	50	50	50
No. requiring i.v. supplement	3	3	4

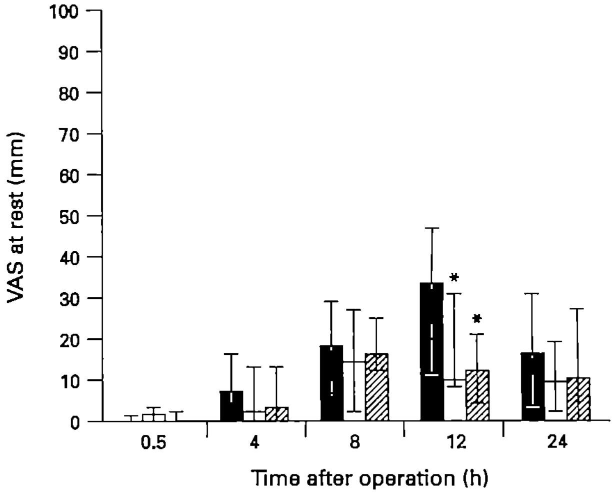


Figure 1 Pain scores (VAS) at rest (median, interquartile range) for groups B (■), F (□) and BF (▨). *$P < 0.05$ compared with group B (Mann–Whitney).

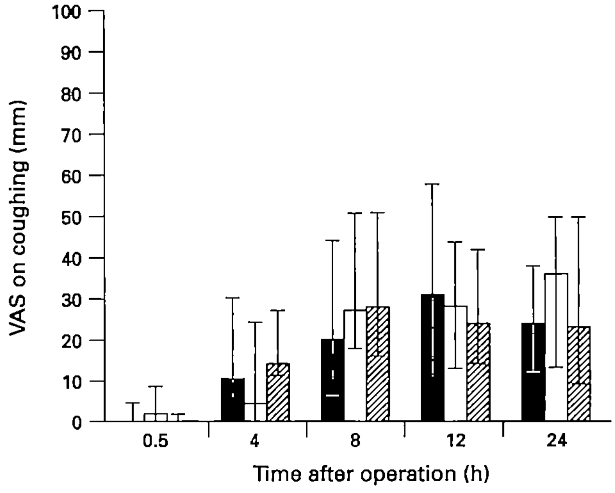


Figure 2 Pain scores (VAS) on coughing (median, interquartile range) for groups B (■), F (□) and BF (▨).

Pain scores at rest are shown in figure 1. At 12 h, group B had higher scores at rest compared with both groups F and BF: group B median 34 (interquartile range (IQR) 11–47) mm, group F 10 (8–31) mm ($P < 0.05$), group BF 12 (4–21) mm ($P < 0.05$). Pain scores on coughing are shown in figure 2. There was no significant difference between the

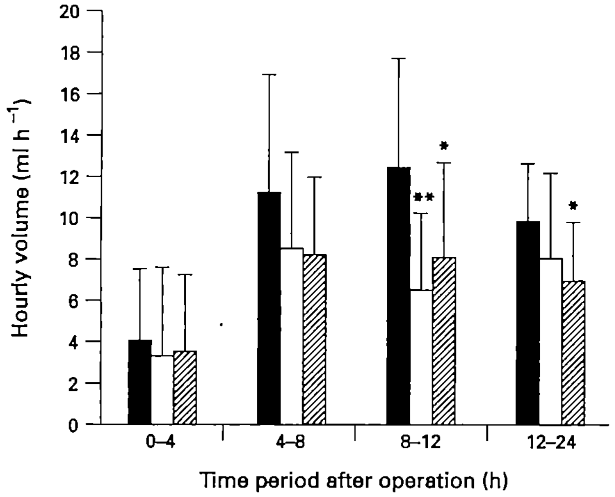


Figure 3 Hourly volumes of solution self-administered (mean, SD) for groups B (■), F (□) and BF (▨). $^*P < 0.05$, $^{**}P < 0.01$ compared with group B (Mann–Whitney).

Table 2 Mean (SD) hourly doses of analgesic solutions administered. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ (Mann–Whitney)

	Group B	Group BF	*P*
Bupivacaine (mg)			
0–4 h	4.0 (3.6)	1.8 (1.9)	
4–8 h	11.1 (5.8)	4.1 (1.9)	**
8–12 h	12.4 (5.3)	4.0 (2.4)	***
12–24 h	9.7 (2.9)	3.5 (1.5)	**
	Group F	Group BF	*P*
Fentanyl (μg)			
0–4 h	12.6 (16.9)	7.0 (7.5)	
4–8 h	33.6 (18.9)	16.3 (7.4)	*
8–12 h	26.1 (14.7)	15.9 (9.4)	
12–24 h	32.1 (16.6)	13.8 (5.9)	***

three groups at any of the assessment times. Pain scores were no lower at rest than on coughing in group B, whereas they were lower at rest in both groups F and BF. Mean pain scores at 8 and 12 h at rest compared with on coughing were as follows: group B 27 (13–33) mm at rest to 24 (10–51) mm on coughing; group F 17 (8–25) mm at rest to 29 (20–35) mm on coughing ($P < 0.01$); group BF 17 (7–20) mm at rest to 26 (16–47) mm on coughing ($P < 0.005$).

Volumes of analgesic solution self-administered are shown in figure 3. Group B had significantly greater PCEA use than both groups F and BF. There was no difference between group F and group BF.

Doses of bupivacaine and fentanyl self-administered are shown in table 2. Combining bupivacaine and fentanyl reduced significantly the doses of both drugs administered. For patients who completed 24 h, overall reductions in the doses of bupivacaine and fentanyl were 62 % and 53 %, respectively. The maximum reduction for bupivacaine (68 %) occurred at 8–12 h and for fentanyl (57 %) at 12–24 h.

The overall incidence of nausea or vomiting was low and there was no significant difference between groups (table 3). All sedation was mild (occasionally drowsy, easy to arouse) apart from one patient in group BF who had moderate sedation (frequently drowsy, easy to arouse). Pruritus was similar for groups F and BF and significantly more frequent than in group B.

Table 3 Incidence (%) of nausea, vomiting, sedation, pruritus, sensory block, motor block, postural hypotension and inability to walk. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with group B; †††$P < 0.001$ compared with group F (Kruskal–Wallis)

	Group B	Group F	Group BF
From 30 min to 24 h	(*n* = 18)	(*n* = 19)	(*n* = 19)
Nausea	11	0	0
Vomiting	6	0	0
Sedation	22	37	21
Pruritus	11	89***	89***
Assessed at end of study	(*n* = 11)	(*n* = 18)	(*n* = 19)
Sensory block	90 (9/10)†††	11	74*†††
Motor block	73	0***	16**
Postural hypotension	0 (0/3)	17	39 (7/18)
Inability to walk	82	24 (4/17)**	53

Eleven patients in group B, 18 in group F and 19 in group BF remained in the study for the full 24 h. Testing for sensory block, motor block, postural hypotension and ability to walk unaided was performed at 20–24 h (table 3).

Maximum sensory block was significantly greater for both groups B (0 = 10 %, 1 = 10 %, 2 = 40 %, 3 = 40 %) and BF (0 = 25 %, 1 = 25 %, 2 = 44 %, 3 = 6 %) than for group F (0 = 89 %, 1 = 11 %). Group B also had significantly greater sensory block than group BF. One of 11 patients in group B was not tested for sensory block.

Motor block was significantly greater for group B (0 = 27 %, 1 = 18 %, 2 = 45 %, 3 = 9 %) compared with group F (0 = 100 %) and group BF (0 = 84 %, 1 = 11 %, 2 = 5 %). The difference between groups F and BF was not significant ($P = 0.08$). The mean dose of bupivacaine administered in group BF at 12–24 h was 4.8 mg h^{-1} for those with leg weakness and 3.2 mg h^{-1} for those without.

Postural hypotension was tested in three patients in group B, 18 in group F and 18 in group BF who were sufficiently free from pain or motor block. Patients were considered to have postural hypotension if they were unable to stand because of dizziness or had a systolic arterial pressure (AP) < 90 mm Hg on attempting to sit or stand. One of three patients in group F with postural hypotension had a recorded AP < 90 mm Hg compared with four of seven patients in group BF with postural hypotension. There was no significant difference between the groups.

A total of 82 % of patients in group B were unable to walk (11 % because of pain, 89 % motor block), 24 % in group F (25 % because of pain, 75 % postural hypotension) and 53 % in group BF (30 % because of motor block, 70 % postural hypotension). The difference between groups B and F was significant but group BF was not significantly different from group B ($P = 0.12$) or group F ($P = 0.08$). One of 18 patients in group F was not tested for mobility.

Minimum postoperative arterial pressure was not significantly different between the three groups and hypotension (AP < 90 mm Hg) was not recorded for any patient other than during testing for postural hypotension. Minimum ventilatory frequency was not significantly different between groups and no patient had a recorded rate of less than 12 bpm.

Verbal rating scores for overall patient satisfaction were significantly poorer for group B (33 % excellent, 28 % adequate, 0 % fair, 39 % poor) compared with both group F (67 % excellent, 28 % adequate, 6 % fair, 0 % poor) ($P < 0.05$) and group BF (63 % excellent, 26 % adequate, 11 % fair, 0 % poor) ($P < 0.05$). There was no significant difference between groups F and BF.

Discussion

Intrathecal local anaesthetics and opioids have been shown to have a synergistic analgesic action in laboratory work [1]. Studies examining extradural analgesia, after abdominal aortic and orthopaedic surgery [7, 8], have shown that combining bupivacaine and fentanyl can result in reductions in doses of the order of 20 % for each drug while maintaining or improving analgesia. Despite these findings several studies have failed to demonstrate any benefit from adding dilute bupivacaine to fentanyl [2–5]. However, evidence increasingly shows that adding solutions of bupivacaine of 0.1 % or greater to fentanyl can either improve analgesia, reduce fentanyl requirements, or both [6–10].

In this study we found a clear overall benefit from adding fentanyl to bupivacaine. It allowed a reduction in bupivacaine dose of up to 68 %, with improved analgesia for rest pain, decreased PCEA use and increased patient satisfaction. As a result of the reduced bupivacaine dose there was less motor and sensory block, but the addition of fentanyl led to an increase in predominantly mild pruritus.

Overall benefits from adding bupivacaine to fentanyl were less apparent. It allowed a reduction in the dose of fentanyl of up to 57 % without altering the low pain scores, PCEA use or the high level of patient satisfaction. However, the decreased dose of fentanyl did not reduce pruritus, whereas the addition of bupivacaine increased sensory block. Clinically significant leg weakness also occurred in 16 % of patients who received 0.05 % bupivacaine. Although the finding was not statistically significant ($P = 0.08$) this was probably a type II error as fentanyl by itself would not be expected to produce motor block. The mean dose of bupivacaine administered during the period that motor block was assessed was only 3.5 mg h^{-1} (4.8 mg h^{-1} for those with leg weakness). This dose was similar to that from two previous studies (approximately 4 mg h^{-1}) which also found problems from bupivacaine-related side effects [10, 11].

Our study also compared bupivacaine alone with fentanyl alone for postoperative analgesia. Bupivacaine produced a similar degree of analgesia on coughing to fentanyl but was less effective at relieving rest pain, even though PCEA use was greater. As a result of inadequate analgesia, 28 % of those receiving bupivacaine, compared with none receiving fentanyl, requested premature cessation of the study. Bupivacaine was also associated with a higher incidence of clinically significant side effects than fentanyl. Sensory block with bupivacaine resulted in two patients stopping early because they found the lack of sensation unpleasant and motor block reduced mobility on the first morning after operation. Of the side effects commonly associated with extradural opioids, there was a high incidence of mild pruritus with fentanyl, but no nausea or vomiting. More effective analgesia, combined with fewer side effects, produced greater patient satisfaction with fentanyl.

The difference in pain scores at rest between bupivacaine and the two fentanyl-containing groups did not occur until 12 h after operation. This may have been because of residual operative analgesia or tachyphylaxis. By 24 h there was again no significant difference. This was probably because of a reduction in the numbers of patients in group B, especially as the majority who stopped early did so because of inadequate analgesia.

At 12 h, when pain scores at rest were significantly lower for each fentanyl-containing group than for bupivacaine alone, pain scores on coughing were similar for all three groups. This suggests that when fentanyl-containing solutions inhibited somatic pain to a similar degree to bupivacaine alone, they were more effective at inhibiting visceral pain. In order to satisfactorily inhibit visceral pain, greater rostral spread of an analgesic solution would be required than to inhibit somatic pain. Lumbar extradural administration of fentanyl can result in detectable cervical CSF concentrations of the drug [12]. A greater degree of rostral spread for fentanyl than for bupivacaine could therefore explain this finding. Pain at rest was similar to pain on coughing within the bupivacaine only group whereas it was lower at rest than on coughing in the fentanyl groups. This could be explained by the same mechanism.

This study has demonstrated an additive analgesic effect between extradural 0.05 % bupivacaine and fentanyl, but it failed to demonstrate any clinical benefit from using the drugs in combination compared with fentanyl alone. Our patients undergoing Caesarean section are mobilized routinely on the first morning after operation and bupivacaine-related side effects that occurred with very low-dose bupivacaine inhibited this process. For postoperative patients where early ambulation is not routine, the improvement in analgesia that can be achieved by adding bupivacaine to fentanyl is more likely to contribute to an overall clinical benefit.

References

1. Maves TJ, Gebhart GF. Antinociceptive synergy between intrathecal morphine and lidocaine during visceral and somatic nociception in the rat. *Anesthesiology* 1992; **76**: 91–99.
2. Badner NH, Reimer EJ, Komar WE, Moote CA. Low-dose bupivacaine does not improve postoperative epidural fentanyl analgesia in orthopedic patients. *Anesthesia and Analgesia* 1991; 72: 337–341.
3. Badner NH, Komar WE. Bupivacaine 0.1 % does not improve

postoperative epidural fentanyl analgesia after abdominal or thoracic surgery. *Canadian Journal of Anaesthesia* 1992; **39**: 330–336.

4. Benzon HT, Wong CA, Wong HY, Brooke C, Wade L. The effect of low-dose bupivacaine on postoperative epidural fentanyl analgesia and thrombelastography. *Anesthesia and Analgesia* 1994; **79**: 911–917.
5. Torda TA, Hann P, Mills G, De Leon G, Penman D. Comparison of extradural fentanyl, bupivacaine and two fentanyl–bupivacaine containing mixtures for pain relief after abdominal surgery. *British Journal of Anaesthesia* 1995; **74**: 35–40.
6. George KA, Wright PMC, Chisakuta A. Continuous thoracic epidural fentanyl for post-thoracotomy pain relief: with or without bupivacaine? *Anaesthesia* 1991; **46**: 732–736.
7. George KA, Chisakuta AM, Gamble JAS, Browne GA. Thoracic epidural infusion for postoperative pain relief following abdominal aortic surgery: bupivacaine, fentanyl or a mixture of both? *Anaesthesia* 1992; **47**: 388–394.
8. Cooper DW, Turner G. Patient-controlled extradural analgesia (PCEA) to compare bupivacaine, fentanyl and bupivacaine with fentanyl in the treatment of postoperative pain. *British Journal of Anaesthesia* 1993; **70**: 503–507.
9. Badner NH, Bhandari R, Komar KE. Bupivacaine 0.125% improves continuous postoperative epidural fentanyl analgesia after abdominal or thoracic surgery. *Canadian Journal of Anaesthesia* 1994; **41**: 387–392.
10. Paech MJ, Westmore MD. Postoperative epidural fentanyl infusion—is the addition of 0.1% bupivacaine of benefit? *Anaesthesia and Intensive Care* 1994; **22**: 9–14.
11. Cohen S, Amar D, Pantuck CB, Pantuck EJ, Weissman AB. Adverse effects of epidural 0.03% bupivacaine during analgesia after Cesarean section. *Anesthesia and Analgesia* 1992; **75**: 753–756.
12. Gourlay GK, Murphy TM, Plummer JL, Kowalski SR, Cherry DA, Cousins MJ. Pharmacokinetics of fentanyl in lumbar and cervical CSF following lumbar epidural and intravenous administration. *Pain* 1989; **38**: 253–259.

British Journal of Anaesthesia 1996; **76**: 616–620

Maternal and uteroplacental haemodynamic state in pre-eclamptic patients during spinal anaesthesia for Caesarean section

J. Karinen, J. Räsänen, S. Alahuhta, R. Jouppila and P. Jouppila

Summary

We have studied the effects of crystalloid (Ringer's acetate 1 litre) preloading and subsequent spinal anaesthesia in 12 pre-eclamptic parturient patients undergoing elective Caesarean section. Maternal placental uterine artery circulation was measured using a pulsed colour Doppler technique with simultaneous measurement of maternal haemodynamic state. Despite preloading, mean maternal systolic arterial pressure (SAP) decreased significantly and marked maternal hypotension (SAP $<$ 80% of baseline value) was recorded in two patients after induction of spinal anaesthesia. Mean central venous pressure increased significantly after preload, but decreased to baseline shortly after induction of spinal anaesthesia. Mean pulsatility index (PI) in the uterine artery did not change during preload or spinal block. In one patient, uterine artery PI increased significantly when SAP decreased to 71% of the baseline value, 14 min after induction of spinal anaesthesia. These results suggest that preload with crystalloid solution does not prevent maternal hypotension in pre-eclamptic patients, and that changes in uterine artery velocity waveforms were minor when SAP was 80% or more of baseline during spinal anaesthesia. These changes did not appear to have any major effect on the clinical condition of the neonate, as assessed by Apgar score and umbilical artery pH values. (*Br. J. Anaesth.* 1996; **76**: 616–620)

Key words

Anaesthesia, obstetric. Blood, flow, feto-uteroplacental. Anaesthetic techniques, subarachnoid.

Pre-eclamptic parturient patients present a challenge to the anaesthetist because of the problems that preeclampsia poses to the fetus and mother. The wellbeing of the fetus is jeopardized by poor placental perfusion which may result from immunologically mediated abnormal trophoblastic invasion or microvascular disease [1] and is reflected as high vascular resistance in the uterine arteries [2]. The mother may develop cardiopulmonary and cerebrovascular emergencies in addition to acute renal failure, severe thrombocytopenia and activation of the coagulation cascade [3].

Extradural anaesthesia is widely accepted as the method of choice for Caesarean section for preeclamptic parturients. There is evidence to suggest that extradural anaesthesia blunts the haemodynamic and neuroendocrine stress responses caused by Caesarean delivery in women with severe preeclampsia [4]. Because uterine blood perfusion is reduced in pre-eclampsia, it is important to prevent maternal hypotension; measures used during regional anaesthesia include left uterine displacement, volume preloading and vasopressor infusion. With these prophylactic measures, it has been shown that plain bupivacaine as an anaesthetic for extradural Caesarean section does not change uteroplacental circulation in hypertensive patients [5].

Severe maternal hypotension is more common during spinal anaesthesia for Caesarean delivery than during extradural anaesthesia. This is one reason why spinal anaesthesia has not been considered widely as an alternative to extradural anaesthesia in pre-eclamptic parturient patients. Preloading and vasopressor infusion did not prevent hypotension during spinal anaesthesia [6, 7]. However, it is crucial to avoid hypotension, especially in pre-eclamptic patients, because of the threat of impaired uterine circulation. We have not found any earlier studies on uteroplacental circulation in preeclamptic patients immediately after induction of spinal anaesthesia. Therefore, in this study we examined the effects of crystalloid preloading and subsequent spinal anaesthesia on maternal, and especially uteroplacental, haemodynamic state in pre-eclamptic patients, using a pulsed colour Doppler technique during the first 20 min of spinal anaesthesia.

Patients and methods

The study was approved by Oulu University Ethics Committee and written informed consent was obtained from each patient. We studied 12 preeclamptic patients (gestation 31–40 weeks) undergoing elective Caesarean section. Of the 12 patients who volunteered for the study, six had severe preeclampsia with an arterial pressure constantly greater than 160/110 mm Hg and proteinuria exceeding 5.0 g 24 h^{-1}. The other six patients had an arterial

---

Juha Karinen, md, Seppo Alahuhta, md, phd, Riitta Jouppila, md, phd (Department of Anaesthesia); Juha Räsänen, md, phd, Pentti Jouppila, md, phd (Department of Obstetrics and Gynaecology); Oulu University Hospital, Kajaanintie 52 A, FIN-90220 Oulu, Finland. Accepted for publication: December 23, 1995.

Correspondence to J.K.

pressure of 140/90–160/110 mm Hg and proteinuria of 0.3–5.0 g 24 h^{-1}. Ten patients were receiving an antihypertensive peroral regimen of labetalol 300–600 mg day^{-1} and one patient was also receiving nifedipine 5–10 mg day^{-1}. None of the patients was in labour. Exclusion criteria included eclampsia, chronic hypertension, chronic renal disease, thrombocytopenia (platelet count < 100000 ml^{-1}) and maternal haemorrhage or signs of fetal distress requiring emergency Caesarean section.

Patients were given 30 ml of sodium citrate 0.3 mol $litre^{-1}$ orally, 60 min before entering the operating theatre, where they were placed in the supine position with a left lateral tilt. Monitoring comprised a three-lead ECG, pulse oxymetry and automated non-invasive arterial pressure (Cardiocap, Datex, Instrumentarium Group, Finland). Oxygen 3 litre min^{-1} was administered via a nasal cannula. A peripheral vein was cannulated for administration of i.v. fluids, and a vein in the right antecubital fossa was cannulated during local anaesthesia with a 16-gauge central venous catheter for continuous monitoring of central venous pressure (CVP) [8]. Correct location of the tip of the CVP catheter was confirmed by recording the CVP waveform. Baseline maternal heart rate (HR), non-invasive systolic (SAP) and diastolic (DAP) arterial pressures and CVP were recorded, and the first Doppler ultrasound examination was performed before i.v preloading. In all patients the bladder was catheterized to measure urine output during Caesarean section.

The maternal uterine artery (main branch on the placental side of the uterus) was identified by colour Doppler near the cervix before its divisions and the blood velocity waveform recorded using the pulsed Doppler method (with a 3.75-MHz sector probe, 120-Hz high-pass filter). Pulsatility index (PI = (systolic peak velocity – end-diastolic velocity)/mean velocity during cardiac cycle) was measured from the blood velocity waveform profile. Three consecutive correctly imaged blood velocity waveforms were analysed and the mean value was used in further analysis. All blood flow velocity waveform recordings were obtained during periods of fetal rest without breathing movements. Maternal HR, SAP, DAP and CVP readings were recorded every 2 min during the study.

After the first Doppler measurement, patients received a preload of crystalloid (Ringer's acetate) solution 1 litre over a 15–20-min period. Immediately after preloading, the second Doppler measurement was obtained. Patients were then placed in a right lateral position, an extradural catheter was inserted 3 cm cephalad through the L1–2 interspace, a 27-gauge spinal needle was inserted into the subarachnoid space at the L3–4 interspace and 0.5 % hyperbaric bupivacaine 2.5 ml (range 2.4–2.6 ml) was injected intrathecally. Patients were then returned to the supine position with a left lateral tilt. Doppler measurements from the same uterine artery were obtained at 2-min intervals during the first 20 min after injection of bupivacaine. Each Doppler measurement required an average of 1 min and was performed by the same obstetrician (J.R.) in every case. During these measurements sensory block was assessed by loss of cold sensitivity and extended to T4 in most patients. After completion of the ultrasound measurements, patients were prepared for surgery. Plain 0.5 % bupivacaine was given later via the extradural catheter if the spinal block began to wear off.

After induction of spinal anaesthesia, crystalloid solution was infused at approximately 1000 ml per 60 min until delivery. The infusion rate of the crystalloid solution was adjusted carefully according to CVP in all subjects to avoid overhydration. The time from induction of spinal anaesthesia to delivery was recorded. Maternal hypotension was defined as a decrease in SAP to 80 % of baseline and was treated by increasing the rate of crystalloid infusion. The minimum percentage value of SAP was recorded. If hypotension was not corrected within 1–2 min, ephedrine 5 mg was injected i.v. repeatedly until SAP was at least 80 % of baseline. A paediatrician assessed the condition of the neonates at delivery using Apgar scores at 1 and 5 min, and blood samples from double-clamped umbilical arteries were obtained immediately after delivery for determination of acid–base status.

Values are presented as mean (SD, range or 95 % confidence intervals (CI)), where appropriate. Values for maternal SAP were also computed as percentage changes from baseline values for later analysis. Paired Student's *t* test was used for evaluation of maximum haemodynamic changes from baseline. Analysis of variance for repeated measures was used to assess the statistical significance of the haemodynamic changes during spinal anaesthesia. The association between the changes in maternal haemodynamic variables and uterine artery PI was assessed by calculating Pearson's correlation coefficient. Differences were considered statistically significant if $P < 0.05$. All statistical tests were performed on a standard PC using the program SPSS for MS Windows release 6.1 (SPSS Inc., USA).

Results

Baseline maternal and newborn data are shown in tables 1 and 2. Mean maternal HR did not change significantly during preloading and spinal anaes-

Table 1 Maternal characteristics (mean (SD or range) or number). Maternal systolic (SAP), mean (MAP) and diastolic (DAP) arterial pressures are mean values 1 day before Caesarean section

	$n = 12$
Maternal	
Age (yr)	27.3 (21–37)
Weight (kg)	73.9 (9.3)
Height (cm)	160.2 (4.9)
SAP (mm Hg)	170.5 (149–194)
MAP (mm Hg)	127.2 (112–141)
DAP (mm Hg)	105.5 (88–125)
Proteinuria (g 24 h^{-1})	6.4 (1—14)
Weeks of pregnancy	34.9 (31–40)
Parity (n)	
Primiparae	5
Multiparae	7

Table 2 Newborn characteristics (mean (range) or number). I–D time = induction of anaesthesia to delivery time. *n = 7

	$n = 12$
Newborn weight (g)	2056 (1160–3825)
Umbilical artery pH*	7.29 (7.14–7.42)
Apgar scores (*n*)	
1 min < 7	2
5 min < 7	0
I–D time (min)	44.8 (29–56)

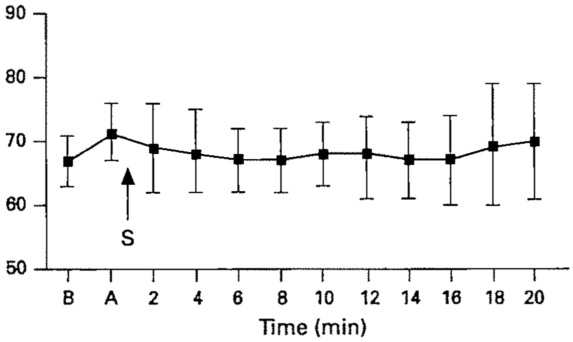


Figure 1 Mean (95 % CI) changes in maternal heart rate (HR) during the study. There were no significant changes. B = Before preload, A = after preload, S = spinal anaesthesia. Time = minutes after injection of intrathecal bupivacaine.

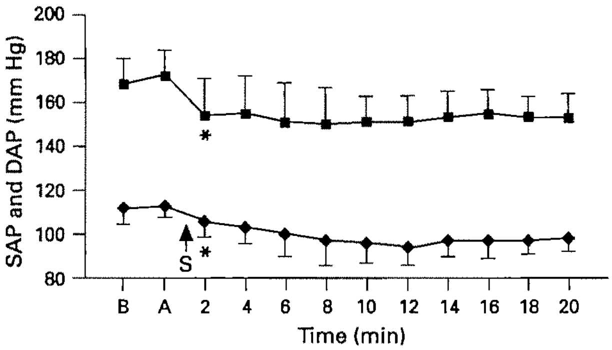


Figure 2 Mean (95 % CI) changes in maternal systolic (SAP) (■) and diastolic (DAP) (◆) arterial pressures during the study. SAP and DAP decreased significantly after induction of spinal anaesthesia (*$P < 0.05$). B = Before preload, A = after preload, S = spinal anaesthesia. Time = minutes after injection of intrathecal bupivacaine.

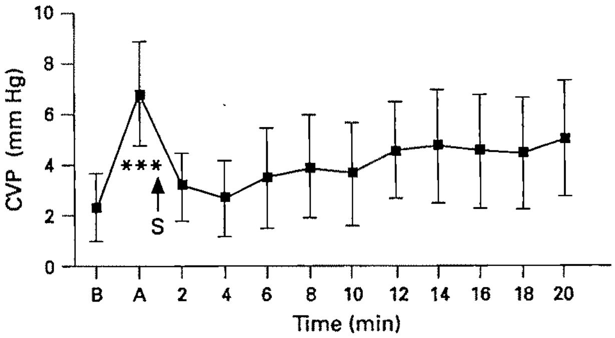


Figure 3 Mean (95 % CI) changes in central venous pressure (CVP) during the study. CVP increased significantly after preload (***$P = 0.001$) and returned towards baseline immediately after induction of spinal anaesthesia. B = Before preload, A = after preload, S = spinal anaesthesia. Time = minutes after injection of intrathecal bupivacaine.

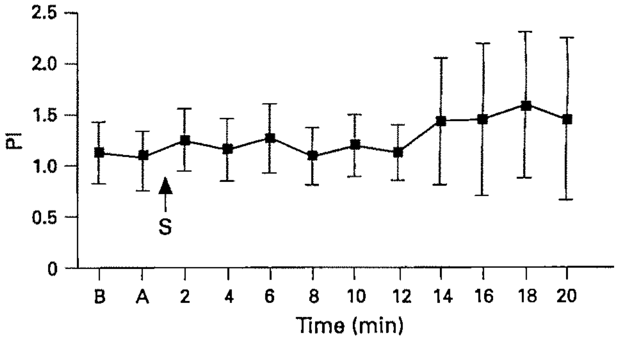


Figure 4 Mean (95 % CI) changes in pulsatility index (PI) of the uterine artery during the study. There were no significant changes. B = Before preload, A = after preload, S = spinal anaesthesia. Time = minutes after injection of intrathecal bupivacaine.

thesia ($P = 0.55$) (fig. 1). Atropine was not required. Mean maternal SAP and DAP decreased significantly after induction of spinal anaesthesia ($P = 0.021$ and 0.017, respectively) (fig. 2). Mean SAP decreased from 169 (95 % CI 157–180) mm Hg to a minimum of 137 (120–154) mm Hg ($P < 0.001$) and mean DAP from 112 (105–118) mm Hg to 90 (79–101) mm Hg ($P < 0.001$) during spinal anaesthesia. The mean maximum percentage decrease in SAP from baseline was 19 (12–26) %. The incidence of maternal hypotension was 17 % (two of 12 patients). Of these two patients, one had marked hypotension and her SAP decreased to 51 % (80 mm Hg) of baseline, 6 min after induction of spinal anaesthesia. In this patient, sensory block extended to C5 and the patient needed assisted ventilation of the lungs with 100 % oxygen via a face mask and a bag for 10–15 min. Oxygen saturation remained at 98–99 %, however, and hypotension responded to the increased crystalloid infusion and ephedrine 10 mg i.v. The patient remained conscious and co-operative and had no convulsions and, therefore, general anaesthesia was not considered. This patient delivered a 1925-g male infant with Apgar scores of 9 and 8 at 1 and 5 min, respectively. Unfortunately, determination of umbilical artery pH was not managed satisfactorily. In the other hypotensive patient, SAP decreased to 71 % (124 mm Hg) of the baseline value and was also corrected rapidly with ephedrine 10 mg.

Mean CVP increased significantly after preloading from 2.3 (95 % CI 1.0–3.7) mm Hg to 6.8 (4.8–8.9) mm Hg ($P < 0.001$) and returned towards baseline values shortly after induction of spinal anaesthesia, after which CVP tended to increase until delivery (fig. 3). In two patients, CVP increased to 10 and 13 mm Hg after preload, but decreased immediately after induction of spinal anaesthesia to 5 and 6 mm Hg, respectively. The total volume of crystalloid infused before delivery was approximately 2108 (range 1500–2400) ml. No patient had any signs of pulmonary oedema during the study.

Mean PI of the uterine artery did not change significantly ($P = 0.28$) during the study (fig. 4) and there was no significant correlation with changes in SAP. In one patient, there was a marked increase in uterine artery PI from 0.73 to 4.22 during a period of maternal hypotension, when SAP decreased to 71 % (124 mm Hg) of baseline, 12 min after induction of spinal anaesthesia. In the case of the most marked decrease in SAP to 51 % of the baseline value, PI of the uterine artery increased from 0.73 to 2.17. We also divided the group into two subgroups of mild and severe pre-eclampsia and found no significant difference in changes in maternal haemodynamic variables (HR, SAP, DAP and CVP) or utero-placental circulation (uterine artery PI) between these subgroups.

Eight of the 12 newborns were small for gestational age (<2.5th percentile). Umbilical artery pH was obtained in seven patients and varied from 7.14 to 7.42. All neonates had Apgar scores of 7 or more at 5 min. After operation, all mothers were observed intensively for the first 24 h, and recovery was uncomplicated in every case.

Discussion

We found reasonably stable maternal and utero-placental haemodynamic values in pre-eclamptic parturient patients undergoing Caesarean section during spinal anaesthesia after prophylactic pre-loading with 1 litre of crystalloid solution. Severe hypotension was seen in only two patients, and this was corrected rapidly by increasing the crystalloid infusion and giving small doses of ephedrine 5–10 mg i.v. However, the absolute mean decrease in SAP in our study was 19 %, which is similar to the decrease of 23 % reported in an earlier study [9]. That retrospective study failed to reveal any significant difference between extradural and spinal anaesthesia for Caesarean section in severely pre-eclamptic parturients with regard to changes in maternal haemodynamics or total intraoperative ephedrine doses used.

The cardiovascular state of severely pre-eclamptic patients has been studied intensively and hyper-dynamic function of the left ventricle has been demonstrated in 73–80 % of patients [10, 11]. In these two studies, there was a normal-to-high cardiac output with inappropriately high peripheral resistance. Cotton and colleagues [11] hypothesized that the increased left ventricular afterload contributes to an increase in pulmonary capillary wedge pressure despite the hypovolaemic state associated with pre-eclampsia and that central venous pressure may therefore reflect the intravascular volume status more accurately than pulmonary capillary wedge pressure. Because none of our patients had pulmonary oedema or persistent oliguria, we used CVP monitoring instead of pulmonary capillary wedge pressure to assess central blood volume during preloading and spinal anaesthesia.

Pre-eclamptic parturients have been shown to suffer from relative hypovolaemia throughout their pregnancy compared with normal parturients [12], and rapid volume expansion with crystalloid [13, 14] or colloid solution [15, 16] has therefore resulted in beneficial effects in pre-eclamptic patients. Infusion of crystalloid solution 15 ml kg^{-1} led to a decrease in systemic vascular resistance [13, 14] and an increase in cardiac output [14] in pre-eclamptic mothers. Infusion of 5 % albumin 500–1000 ml [15] or 3.5 % colloid plasma substitute 200–600 ml [16] also resulted in an increase in cardiac index and a decrease in systemic vascular resistance. After rapid volume expansion, mean SAP was unchanged [16] or slightly reduced [15]. Grunewald and colleagues [13] demonstrated no change in uterine artery PI after rapid volume expansion. Hence, volume expansion in pre-eclamptic patients with either crystalloid or colloid solution appears to be a reasonable first measure to restore central blood volume and to stabilize maternal haemodynamic state, especially before induction of central neural block. In our study, mean initial CVP was 2.3 mm Hg, it increased markedly to 6.8 mm Hg after volume expansion and remained slightly less than 6 mm Hg after induction of spinal anaesthesia. These stable values during spinal anaesthesia, which were at physiological normal levels, imply that spinal block did not significantly affect maternal central blood volume in pre-eclamptic patients, as there were no large alterations in CVP.

Mean maternal HR did not change significantly during the study despite the significant decrease in SAP. There is at least one potential explanation for this stability. Of the 12 patients in our study, 10 were using labetalol. This drug may have prevented a compensatory increase in maternal HR. Labetalol, on the other hand, does not appear to affect uteroplacental blood flow in pre-eclampsia [17, 18].

Robson and colleagues [19] have reported a decrease in uteroplacental blood flow secondary to reduced maternal cardiac output and stroke volume during spinal anaesthesia in healthy parturients. In this study, uterine artery PI values did not change significantly during preload or spinal anaesthesia. This is in contrast with our recent findings [20], which demonstrated occasionally high but transient increases in uterine artery PI in some healthy parturients during spinal anaesthesia. These increases, which reflected increased vascular resistance, did not, however, relate to any obvious changes in individual maternal SAP, HR, or CVP. This difference in the changes in uterine artery resistance (PI) between normal and pre-eclamptic parturients was surprising, and we can only speculate on the underlying reasons. Although we did not have a control group in this study, we are able to compare our results with those of an earlier study by our team using extradural anaesthesia [5]. In that study, Alahuhta and colleagues demonstrated no change in uterine artery PI in hypertensive mothers with chronic fetal asphyxia after extradural anaesthesia with plain bupivacaine and no patient had profound hypotension or required a vasopressor. Eneroth-Grimfors and colleagues [21] observed decreased vagal control of the heart in pre-eclampsia. These changes in the cardiovascular state of pre-eclampsia together with the α and β blocking agent, labetalol, used by the majority of our patients may account for the different results obtained in healthy and pre-eclamptic parturients during spinal anaesthesia.

Our finding, that uteroplacental blood flow did not change markedly during spinal anaesthesia, is in accordance with our earlier data [22]. In that study, placental blood flow, recorded with an isotope technique, did not change in seven healthy parturients and even increased in one patient with pre-eclampsia during spinal anaesthesia. In the 12 pre-eclamptic patients in this study, a marked increase in uterine artery PI as a sign of increased vascular resistance was seen in only one patient simultaneously with a period of severe hypotension lasting 4–6 min after induction of spinal anaesthesia. This was, however, corrected promptly with adequate measures. In the other patient, with even more marked hypotension, uterine artery PI increased only slightly and normalized rapidly. It seems therefore that PI levels in uterine arteries are stable and not sensitive to a moderate decrease in maternal arterial pressure. The good condition of the neonates was a further indication of undisturbed uterine haemodynamic state during the study. The small number of pre-eclamptic subjects examined here may, however, have limited the possibility of observing significant changes in uterine artery PI values after marked maternal hypotension.

Acknowledgement

We thank Mr Kauko Korpi, RN, for his valuable assistance in the operating theatre.

References

1. Roberts JM, Redman CWG. Pre-eclampsia: more than pregnancy-induced hypertension. *Lancet* 1993; **341**: 1447–1451.
2. Olofsson P, Laurini RN, Marsál K. A high uterine artery pulsatility index reflects a defective development of placental bed spiral arteries in pregnancies complicated by hypertension and fetal growth retardation. *European Journal of Obstetrics and Gynecology and Reproductive Biology* 1993; **49**: 161–168.
3. Ramanathan J. Pathophysiology and anesthetic implications in preeclampsia. *Clinical Obstetrics and Gynecology* 1992; **35**: 414–425.
4. Ramanathan J, Coleman P, Sibai B. Anesthetic modification of hemodynamic and neuroendocrine stress responses to Caesarean delivery in women with severe preeclampsia. *Anesthesia and Analgesia* 1991; **73**: 772–779.
5. Alahuhta S, Räsänen J, Jouppila P, Jouppila R, Hollmén AI. Uteroplacental and fetal circulation during extradural bupivacaine–adrenaline and bupivacaine for Caesarean section in hypertensive pregnancies with chronic fetal asphyxia. *British Journal of Anaesthesia* 1993; **71**: 348–353.
6. Rout CC, Akoojee SS, Rocke DA, Gouws E. Rapid administration of crystalloid preload does not decrease the incidence of hypotension after spinal anaesthesia for elective Caesarean section *British Journal of Anaesthesia* 1992; **68**: 394–397.
7. Olsen KS, Feilberg VL, Hansen CL, Rudkjobing O, Pedersen T, Kyst A. Prevention of hypotension during spinal anaesthesia for Caesarean section. *International Journal of Obstetric Anaesthesia* 1994; **3**: 20–24.
8. Gustavsson B, Linder LE, Hultman E, Curelaru I. "Halfway" venous catheters. I. Theoretical premises and aims. *Acta Anaesthesiologica Scandinavica* 1985; (Suppl. 81): 30–31.
9. Hood DD, Boese PA. Epidural and spinal anesthesia for elective Cesarean section in severely pre-eclamptic parturients. *Regional Anesthesia* 1992; **17** (Suppl. 1): 35.
10. Mabie WC, Ratts TE, Sibai BM. The central hemodynamics of severe preeclampsia. *American Journal of Obstetrics and Gynecology* 1989; **161**: 1443–1448.
11. Cotton DB, Lee W, Huhta JC, Dorman KF. Hemodynamic profile of severe pregnancy-induced hypertension. *American Journal of Obstetrics and Gynecology* 1988; **158**: 523–529.
12. Hays PM, Cruikshank DP, Dunn LJ. Plasma volume determination in normal and preeclamptic pregnancies. *American Journal of Obstetrics and Gynecology* 1985; **151**: 958–966.
13. Grunewald C, Nisell H, Carlström K, Kublickas M, Randmaa I, Nylund L. Acute volume expansion in normal pregnancy and preeclampsia. Effects of plasma atrial natriuretic peptide (ANP) and cyclic guanosine monophosphate (cGMP) concentrations and feto-maternal circulation *Acta Obstetricia et Gynecologica Scandinavica* 1994; **73**: 294–299.
14. Nisell H, Carlström K, Cizinsky S, Grunewald C, Nylund L, Randmaa I. Atrial natriuretic peptide concentrations and hemodynamic effects of acute plasma volume expansion in normal pregnancy and preeclampsia *Obstetrics and Gynecology* 1992; **79**: 902–907.
15. Wasserstrum N, Kirshon B, Willis RS, Moise KJ, Cotton DB. Quantitative hemodynamic effects of acute volume expansion in severe preeclampsia. *Obstetrics and Gynecology* 1989;**73**: 546–550.
16. Belfort M, Uys P, Dommisse J, Davey DA. Haemodynamic changes in gestational proteinuric hypertension: the effects of rapid volume expansion and vasodilator therapy. *British Journal of Obstetrics and Gynaecology* 1989; **96**: 634–641.
17. Jouppila P, Kirkinen P, Koivula A, Ylikorkala O. Labetalol does not alter the placental and fetal blood flow or maternal prostanoids in pre-eclampsia. *British Journal of Obstetrics and Gynaecology* 1986; **93**: 543–547.
18. Pickles CJ, Symonds EM, Pipkin FB. The fetal outcome in a randomized double-blind controlled trial of labetalol versus placebo in pregnancy-induced hypertension. *British Journal of Obstetrics and Gynaecology* 1989; **96**: 38–43.
19. Robson SC, Boys RJ, Rodeck C, Morgan B. Maternal and fetal haemodynamic effects of spinal and extradural anaesthesia for elective Caesarean section. *British Journal of Anaesthesia* 1992; **68**, 54–59.
20. Karinen J, Räsänen J, Alahuhta S, Jouppila R, Jouppila P. Effect of crystalloid and colloid preloading on uteroplacental and maternal haemodynamic state during spinal anaesthesia for Caesarean section. *British Journal of Anaesthesia* 1995; **75**: 531–535.
21. Eneroth-Grimfors E, Westgren M, Ericson M, Ihrman-Sandahl C, Lindblad LE. Autonomic cardiovascular control in normal and pre-eclamptic pregnancy. *Acta Obstetricia et Gynecologica Scandinavica* 1994; **73**: 680–684.
22. Jouppila P, Jouppila R, Barinoff T, Koivula A. Placental blood flow during Caesarean section performed under subarachnoid blockage *British Journal of Anaesthesia* 1984; **56**:1379–1383.

British Journal of Anaesthesia 1996; **76**: 621–623

Effect of antagonism of mivacurium on recovery of extraocular muscle function

D. J. MELLOR, E. MOSS, E. M. MCATEER AND M. V. SHAH

Summary

We have measured extraocular muscle function in 41 patients who received neuromuscular block with mivacurium 0.2 mg kg^{-1} during anaesthesia with propofol, ketorolac, fentanyl and isoflurane in nitrous oxide and oxygen, which was antagonized at the end of surgery with neostigmine 0.05 mg kg^{-1} and glycopyrronium 0.01 mg kg^{-1} in 21 of these patients. Extraocular muscle function was measured before and after surgery in each group with the Maddox Wing apparatus and compared with a control group ($n = 20$) who breathed spontaneously the same gaseous anaesthetic mixture via a reinforced laryngeal mask airway. In patients where the action of mivacurium was antagonized, extraocular muscle function was improved significantly 20 min after antagonism ($P < 0.001$) compared with those who received no antagonism. At 60 min after antagonism, there were no differences between the groups. There were no differences between patients who received no neuromuscular blockers and those who received blocker and antagonist. (*Br. J. Anaesth.* 1996; **76**: 621–623)

Key words

Neuromuscular block, mivacurium. Neuromuscular block, antagonism. Eye, extraocular muscles.

Mivacurium is a new non-depolarizing neuromuscular blocking agent with a short duration of action and rapid offset of effect because of its rapid metabolism by plasma cholinesterase. This occurs *in vitro* at approximately 80% of the rate at which suxamethonium is degraded [1, 2].

The rapid recovery from mivacurium-induced neuromuscular block allows patients to recover from the block without the use of anticholinesterase drugs [3]. However, there is wide inter-patient variability in response to neuromuscular block with mivacurium [2] and neuromuscular monitoring should be used to demonstrate satisfactory antagonism of its effects before termination of anaesthesia.

Traditionally, recovery from neuromuscular block is monitored by train-of-four stimulation. However, in clinical anaesthesia, the train-of-four is observed visually and is a relatively poor indicator of recovery [4].

The ability of neostigmine to antagonize neuromuscular block produced by mivacurium has been demonstrated [1] using train-of-four stimulation and electromyogram recording or adductor pollicis force transduction [3]. However, neostigmine blocks the metabolism of mivacurium *in vitro* in a dose-dependent manner [5]. This has been demonstrated *in vivo* with prolongation of intense mivacurium-induced block by administration of neostigmine [6]. Faced with the difficulty of measuring subtle degrees of muscular weakness, many anaesthetists use neostigmine to antagonize any residual effects of mivacurium after anaesthesia. Our study aimed to demonstrate the benefit of this practice, using the Maddox Wing apparatus to detect residual neuromuscular dysfunction.

Patients and methods

After obtaining Ethics Committee approval and informed consent, we studied 61 patients undergoing day-case anaesthesia for minor oral surgery. Patients were allocated randomly to one of three groups by choosing sealed envelopes.

The Maddox Wing is a device used by orthoptists to measure latent squint. It consists of a black metal screen with baffles to present an image of two perpendicular arrows to the right eye. The left eye is presented with an image of two perpendicular scales. These are graduated in prism dioptres and the amount of esophoria or exophoria is the number on the horizontal scale where the arrow is superimposed onto the scale. Before surgery, the visual function of each subject was tested with the Maddox Wing apparatus. Esophoria and exophoria were recorded, as measured on the horizontal scale of the Maddox Wing. No results were recorded from the vertical scale. No premedication was used and patients requiring spectacles for refractive correction were allowed to use them.

After attaching full monitoring, anaesthesia was induced with propofol 2.5 mg kg^{-1} i.v. Each 20-ml syringe of propofol contained lignocaine 10 mg to relieve pain on injection. Each patient received fentanyl 1 μg kg^{-1} and ketorolac 10 mg i.v. At termination of anaesthesia, ketorolac 20 mg was administered.

D. J. MELLOR, BSC, MB, BS, FRCA, E. MOSS, MB, CHB, MD, FRCA, E. M. MCATEER, MB, BCH, FFARCSI, M. V. SHAH, MRCS, LRCP, FRCA, Department of Anaesthetics, Leeds General Infirmary, Great George Street, Leeds LS1 3EX. Accepted for publication: January 5, 1996.

Patients in groups MIV and REV were given mivacurium 0.2 mg kg^{-1} at induction of anaesthesia. The trachea was intubated via the nasal route and the lungs ventilated to normocapnia with 1–2 % inspired isoflurane and 66 % nitrous oxide in oxygen. The time of administration of mivacurium was recorded as time A. At termination of surgery, isoflurane was discontinued and neostigmine 0.05 mg kg^{-1} and glycopyrronium 0.01 mg kg^{-1} administered to group REV. The time of antagonism and discontinuing isoflurane was recorded as time B.

Patients in the laryngeal mask airway (LMA) group were used as a control; these patients did not receive mivacurium or a reversal agent. Time A was recorded as the time of administration of propofol 2.5 mg kg^{-1}. Fentanyl 1 μg kg^{-1} and ketorolac 10 mg, followed by 20 mg after operation, were administered and an LMA inserted. Patients breathed a mixture of 1–2 % isoflurane and 66 % nitrous oxide in oxygen. Time B was recorded at termination of surgery when isoflurane was discontinued.

At the end of anaesthesia in groups MIV and REV, neuromuscular function was assessed using a peripheral nerve stimulator before waking the patient to ensure against prolonged neuromuscular block caused by atypical plasma cholinesterase. A train-of-four count of four twitches with no fade was taken as demonstrating adequate antagonism.

Extraocular muscle function was tested 45 min after time A, and 20 and 60 min after time B. Visual function was tested by the same observer who performed the preoperative test, who was blinded to the anaesthetic technique used.

As the data were not from a normally distributed population, visual disturbance in prism dioptres for the three treatment groups was tested with the Kruskal–Wallis one-way analysis of variance and the Mann-Whitney *U* test. $P < 0.05$ was considered significant.

Results

Three patients were excluded from the study, one because of uniocular blindness, one because of severe squint, unsuccessfully corrected by surgery and one because of excessive sleepiness after anaesthesia. The mean duration of anaesthesia was 23 min and there were no significant differences in operative time between the groups (table 1). The values obtained 45 min after time A and 20 min after time B were similar.

The mean preoperative degree of exophoria did not differ significantly between the three groups (Kruskal–Wallis) (table 1).

Table 1 Median (range) operation time and preoperative visual function in the groups in which neuromuscular block was (REV) and was not (MIV) antagonized, and in the laryngeal mask airway (LMA) control group. No significant differences between groups

Group	*n*	Operation time (min)	Preop. exophoria (prism dioptres)
REV	21	23 (10–45)	2 (0–10)
MIV	20	22 (10–61)	2 (0–6)
LMA	20	25 (8–33)	2 (0–10)

Table 2 Median (range) change in visual function (exophoria) 45 min after induction of anaesthesia (A45) and 20 (B20) and 60 (B60) min after antagonism of neuromuscular block or completion of anaesthesia

Group	A45	B20	B60
REV	6 (0–14)	4 (0–12)	2 (0–6)
MIV	12 (4–16)	12 (6–16)	4 (0–6)
LMA	6 (0–29)	6 (0–29)	2 (0–12)
P (MIV *vs* LMA)	< 0.01	< 0.001	ns
P (REV *vs* LMA)	ns	ns	ns
P (MIV *vs* REV)	< 0.001	< 0.001	ns

Table 2 shows the degree of exophoria measured after operation. The values shown were corrected by subtracting the degree of pre-existing exophoria from the postoperative result. A45 is the change at 45 min after induction time A. B20 and B60 are the changes at 20 and 60 min after reversal time B.

When group MIV and both groups REV and LMA were compared, there were significant differences at both times A45 and B20. There were no significant differences between groups REV and LMA. There were no significant differences between the groups at time B60.

Discussion

The Maddox Wing apparatus has been used in several studies of postoperative recovery. Its use as a test of recovery from general anaesthesia was first described in 1970 [7]. It is a simple, non-painful test to perform in the immediate postoperative period.

Recovery from anaesthesia is a multidimensional phenomenon in the same way that a balanced anaesthetic consists of components of anaesthesia, analgesia and paralysis. The Maddox Wing has been used as an indicator of residual paralysis [8, 9] comparing one neuromuscular blocker with another. In an analysis of six recovery tests [10] the Maddox Wing was used as an indicator of sedation. It has been used to assess sedation after propofol infusions [11] and alcohol consumption [12]. As far as we are aware, the Maddox Wing has not been used to monitor the effects of reversal drugs on extraocular muscle function.

In designing a study to demonstrate neuromuscular dysfunction using the Maddox Wing, it is crucial to eliminate the effects caused by sedative agents. For this reason we included a control group (LMA) who received neither mivacurium nor reversal agents, breathing spontaneously the same gaseous anaesthetic mixture via a reinforced laryngeal mask airway.

Our results demonstrated significant changes in extraocular muscle function in the hour after anaesthesia. Of note was the significant ($P < 0.001$) difference in the early postoperative period between those treated with mivacurium and those who received mivacurium and antagonism. This was demonstrated at 20 min after termination of anaesthesia (B20) and at 45 min after the start of anaesthesia (A45). At 20 min after operation, there was significantly less exophoria in the LMA group than in those who received mivacurium alone ($P < 0.001$).

Our results suggest an improvement in extraocular muscle function in the first hour after operation in patients whose mivacurium block was antagonized by neostigmine and glycopyrronium. This improvement may result from antagonism of acetylcholinesterase at the neuromuscular junction.

Neostigmine is well known to have central effects on cholinergic receptors, despite poor penetration of the blood–brain barrier. It also has an effect on cholinergic transmission in the eye [13]. It is not possible to rule out the central, analeptic effects of neostigmine, the peripheral cholinergic effects of miosis and accommodation caused by neostigmine as explanations of our findings. Glycopyrronium should antagonize these effects but it also poorly penetrates the blood–brain barrier.

Recovery of neuromuscular function has been shown to be more rapid after antagonism with neostigmine from both bolus doses and infusions of mivacurium [2]. However, there is evidence to support withholding anticholinesterase drugs. Patients undergoing laparoscopic surgery receiving mivacurium followed by antagonism with neostigmine have been shown to have a greater incidence of nausea and vomiting compared with patients receiving no antagonism [14]. This effect was also demonstrated in children [15]. We did not specifically examine postoperative nausea and vomiting in our study. In another study using mivacurium without antagonism for outpatient dentoalveolar surgery, the incidence of nausea and vomiting was 6% [unpublished results].

In addition, neostigmine antagonizes plasma cholinesterase [5, 16]. Thus in the presence of high degrees of block, corresponding to high concentrations of unmetabolized mivacurium, administration of neostigmine may paradoxically increase recovery time. This effect may result from development of channel block.

In each of our three groups, extraocular muscle function was the same 1 h after anaesthesia, which indicates spontaneous recovery from minor degrees of neuromuscular block. Spontaneous recovery of mivacurium-induced neuromuscular block has been demonstrated to be safe, allowing adequate neuromuscular function for spontaneous respiration and airway maintenance [3]. However, our results showed that antagonism of an intubating dose of mivacurium significantly improves extraocular muscle function during the first hour after operation, which indicates improved antagonism of subtle degrees of neuromuscular block. The clinical benefit of achieving this degree of antagonism of a single dose of mivacurium in patients undergoing day-case surgery is debatable.

References

1. Baurain BJ, Dernovoi BS, D'Hollander AA, Hennart DA. Comparison of neostigmine-induced recovery with spontaneous recovery from mivacurium-induced neuromuscular block. *British Journal of Anaesthesia* 1994; 73: 791–794.
2. Savarese JJ, Hassan HA, Salvatore JB, Embree PB, Scott RPF, Sunder N, Weakly JN, Wastila WB. The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U): a short acting nondepolarising ester neuromuscular blocking drug. *Anesthesiology* 1988; **68**: 723–732.
3. Brull SJ, Conelly NR, Silverman DG. Recovery of train of four after mivacurium. *Canadian Journal of Anaesthesia* 1995; 42: 28–31.
4. Viby-Morgensen J, Jensen NH, Engbaek J, Ording H, Skovgaard LT, Chraemmer-Jorgensen B. Tactile and visual evaluation of the response to train of four nerve stimulation. *Anesthesiology* 1985; **63**: 440–443.
5. Cook DR, Chakravorti S, Brandom BW, Stiller RL. Effects of neostigmine, edrophonium and succinylcholine on the in-vitro metabolism of mivacurium chloride: clinical correlates. *Anesthesiology* 1992; 77: A948.
6. Abdulatif M. Recovery characteristics after early administration of anticholinesterases during intense mivacurium induced neuromuscular block. *British Journal of Anaesthesia* 1995; 74: 20–25.
7. Hannington-Kiff JG. Measurement of recovery from outpatient general anaesthesia with a simple ocular test. *British Medical Journal* 1970; 3: 132–135.
8. Sosis M, Goldberg ME, Marr AT, Cubler AJ, Larijani GE. Atracurium and vecuronium do not affect extraocular muscle function after out-patient surgery. *Anesthesiology* 1988; **68**: 465–468.
9. Zuurmond WWA, van Leeuwen L. Atracurium versus vecuronium: a comparison of recovery in outpatient arthroscopy. *Canadian Journal of Anaesthesia* 1988; 35: 139–142.
10. Zuurmond WWA, Balk VA, vanDis H, van Leeuwen L, Paul EAA. Multidimensionality of psychological recovery from anaesthesia. *Anaesthesia* 1989; 44: 889–892.
11. Zuurmond WWA, van Leeuwen L, Helmers JHJH. Recovery from propofol infusion as the main agent for outpatient arthroscopy. A comparison with isoflurane. *Anaesthesia* 1987; 42: 356–359.
12. Thapar P, Zacny JP, Thompson W, Apfelbaum JL. Using alcohol as a standard to assess the degree of impairment induced by sedative and analgesic drugs used in ambulatory surgery. *Anesthesiology* 1995; 82: 53–59.
13. Bevan DR, Donati F, Kopman AF. Reversal of neuromuscular blockade. *Anesthesiology* 1992; 77: 785–805.
14. Ding Y, Fredman B, White PF. Use of mivacurium during laparoscopic surgery: Effect of reversal drugs on postoperative recovery. *Anesthesia and Analgesia* 1994; 78: 450–454.
15. Watcha MF, Safavi FZ, McCulloch DA, Tan TSH, White PF. Effect of antagonism of mivacurium induced neuromuscular block on post-operative emesis in children. *Anesthesia and Analgesia* 1995; 80: 713–717.
16. Connoly FM, Mirakhur RK, Loan PB, McCoy EP, Symington M, Kumar N. Antagonism of mivacurium block with edrophonium from various degrees of spontaneous recovery. *British Journal of Anaesthesia* 1995; 74: 229–230.

British Journal of Anaesthesia 1996; **76**: 624–628

Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation†

A. M. De Wolf, J. A. Freeman, V. L. Scott, W. Tullock, D. A. Smith, D. F. Kisor, S. Kerls and D. Ryan Cook

Summary

We determined the pharmacokinetics and pharmacodynamics of cisatracurium, one of the 10 isomers of atracurium, in 14 patients with end-stage liver disease undergoing liver transplantation and in 11 control patients with normal hepatic and renal function undergoing elective surgery. Blood samples were collected for 8 h after i.v. bolus administration of cisatracurium 0.1 mg kg^{-1} (2 × ED$_{95}$). Plasma concentrations of cisatracurium and its metabolites were determined using an HPLC method with fluorescence detection. Pharmacokinetic variables were determined using non-compartmental methods. Neuromuscular block was assessed by measuring the electromyographic evoked response of the adductor pollicis muscle to train-of-four stimulation of the ulnar nerve using a Puritan–Bennett Datex (Helsinki, Finland) monitor. Pharmacodynamic modelling was completed using semi-parametric effect-compartment analysis. Volume of distribution at steady state was 195 (SD 38) ml kg^{-1} in liver transplant patients and 161 (23) ml kg^{-1} in control patients ($P < 0.05$), plasma clearance was 6.6 (1.1) ml kg^{-1} min^{-1} in liver transplant patients and 5.7 (0.8) ml kg^{-1} min^{-1} in control patients ($P < 0.05$), but elimination half-lives were similar: 24.4 (2.9) min in liver transplant patients *vs* 23.5 (3.5) min in control patients (ns). The time to maximum block was 2.4 (0.8) min in liver transplant patients compared with 3.3 (1.0) min in control patients ($P < 0.05$), but the clinical effective duration of action (time to 25% recovery) was similar: 53.5 (11.9) min in liver transplant patients compared with 46.9 (6.9) min in control patients (ns). The recovery index (25–75% recovery) was also similar in both groups: 15.4 (4.2) min in liver transplant patients and 12.8 (1.9) min in control patients (ns). After cisatracurium, peak laudanosine concentrations were 16 (5) and 21 (5) ng ml^{-1} in liver transplant and control patients, respectively. In summary, minor differences in the pharmacokinetics and pharmacodynamics of cisatracurium in liver transplant and control patients were not associated with any clinically significant differences in recovery profiles after a single dose of cisatracurium. (*Br. J. Anaesth.* 1996; **76**: 624–628)

Key words

Neuromuscular block, 51W89. Neuromuscular block, atracurium. Pharmacokinetics, 51W89. Pharmacokinetics, atracurium. Pharmacokinetics, stereoisomers. Pharmacodynamics. Liver, disease. Liver, transplantation.

Cisatracurium besylate (51W89; NIMBEX), one of the 10 isomers of atracurium, is approximately three times more potent than atracurium, with an ED$_{95}$ of 0.05 mg kg^{-1} [1], a similar neuromuscular blocking profile to that of atracurium except for a slower onset [1–4] and less propensity to release histamine than atracurium [5]. Cisatracurium undergoes spontaneous degradation in the body at physiological pH and temperature by organ-independent Hofmann elimination to form laudanosine and a monoquaternary acrylate metabolite. The monoquaternary acrylate metabolite undergoes hydrolysis by non-specific plasma esterases to form a monoquaternary alcohol [6]. Hydrolysis of cisatracurium by plasma esterases is not an important pathway for elimination of cisatracurium [6]. In contrast, atracurium is eliminated by Hofmann degradation and hydrolysis by non-specific esterases [7, 8].

Although cisatracurium predominantly undergoes spontaneous degradation by Hofmann elimination [6, 9], liver disease may be associated with changes in the pharmacokinetics, pharmacodynamics, or both, of cisatracurium. In this study, we evaluated the safety, pharmacokinetics and pharmacodynamics of cisatracurium in adults with end-stage liver disease undergoing liver transplan-

---

Andre M. De Wolf*, MD, Judith A. Freeman, MD, Victor L. Scott, MD, William Tullock, MD, D. Ryan Cook, MD, Department of Anesthesiology and Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA. Deborah A. Smith, PharmD (Department of Clinical Pharmacokinetics/Dynamics); David F. Kisor, PharmD (Division of Pharmacokinetics and Drug Metabolism); Susan Kerls, BS (Department of Clinical Neurosciences); Glaxo Wellcome, Research Triangle Park, NC, USA. Accepted for publication: December 14, 1995.

*Address for correspondence: Department of Anesthesiology and Critical Care Medicine, Room C-222, Presbyterian University Hospital, University of Pittsburgh Medical Center, 200 Lothrop Street, Pittsburgh, PA 15213-2582, USA.

†Presented in part at the American Society of Anesthesiology meeting, San Francisco, October 19, 1994.

tation and in adults with normal kidney and liver function undergoing elective surgery (control patients).

Patients and methods

We studied 25 (18 men) surgical patients, aged 19–65 yr, after obtaining approval from the hospital Institutional Research Review Board and informed written consent from each patient. Fourteen patients (ASA III or IV) had end-stage liver disease and were undergoing liver transplantation; 11 patients (ASA I or II) without known hepatic or renal disease served as controls. Patients in the liver transplantation group did not have clinical evidence of renal insufficiency, although glomerular filtration rate was not determined; the highest serum creatinine concentration was 140 μmol litre^{-1}. Patients did not receive aminoglycoside antibiotics within 48 h of the study or antihistamine drugs within 8 h of the study, and none had any disease known to affect neuromuscular transmission. Age, weight and laboratory data for both groups are summarized in table 1.

Anaesthesia was induced with thiopentone 4.8 (SD 1.3) mg kg^{-1} and fentanyl 4.4 (2.6) μg kg^{-1}. In addition, 17 of 25 patients received midazolam 0.026 (0.016) mg kg^{-1} before induction of anaesthesia. Tracheal intubation was facilitated by administration of suxamethonium 1.3 (0.7) mg kg^{-1}. Anaesthesia was maintained with isoflurane (0.5 % end-tidal concentration) and 50–70 % nitrous oxide in oxygen. Incremental doses of fentanyl were given if needed. Ventilation was controlled to maintain end-tidal $P\text{CO}_2$ at 4.6–5.3 kPa. Arterial pressure was monitored directly using an indwelling radial arterial cannula. Body temperature was maintained at 35.0–37.5 °C.

After induction of anaesthesia, neuromuscular function was monitored by supramaximal stimulation of the ulnar nerve at the wrist with repetitive train-of-four stimuli (0.2-ms square waves at a frequency of 2 Hz for 2 s at 20-s intervals) using surface electrodes. The evoked compound electromyogram of thumb adduction (adductor pollicis) was recorded using a Puritan–Bennett Datex (Helsinki, Finland) monitor. After full recovery of neuromuscular transmission from suxamethonium and re-establishment of a baseline evoked response, a single bolus injection of cisatracurium 0.1 mg kg^{-1} (2 × ED$_{95}$) was administered via an i.v. cannula over a 5–10-s period. The degree of neuromuscular block was described as percentage of control; the height of the first train-of-four response (T1) was compared with the baseline T1 response (T0). Time from injection of cisatracurium to maximum neuromuscular block and the times for T1:T0 to reach 5 %, 25 %, 75 % and 95 % were noted from the tracings. The time for T1:T0 to reach 25 % was considered to be the clinically effective duration of action. Recovery indices (time for T1:T0 to recover from 25 % to 75 % and from 5 % to 95 %) and the time to T4:T1 $\geqslant$ 70 % were calculated from these data.

Table 1 Patient characteristics and preoperative clinical laboratory data (mean (SD or range)). ALP = Alkaline phosphatase; AST = aspartate transaminase; ALT = alanine transaminase. *$P < 0.05$ compared with liver transplant patients.

	Liver transplant patients (n = 14)	Control patients (n = 11)
Age (yr)	48 (19–65)	37 (21–65)*
Weight (kg)	81 (26)	80 (12)
Haemoglobin (g litre^{-1})	122 (27)	131 (16)
Creatinine (μmol litre^{-1})	80 (35)	80 (27)
ALP (iu litre^{-1})	233 (215)	69 (24)*
AST (iu litre^{-1})	139 (184)	36 (25)
ALT (iu litre^{-1})	74 (41)	49 (43)
Bilirubin (μmol litre^{-1})	75 (63)	10 (3)*
Albumin (g litre^{-1})	30 (9)	39 (5)*

Arterial blood samples (5 ml) were collected before (time 0) and 2, 4, 6, 8, 10, 12, 15, 20, 25, 30, 45, 60, 90, 120, 240 and 480 min after administration of *cis*-atracurium. Blood samples were added to chilled tubes containing ethylenediamine tetra-acetic acid (EDTA), mixed thoroughly, and centrifuged; 1-ml aliquots of plasma were added to 4.0 ml of sulphuric acid 15 mmol litre^{-1} within 3 min of blood sample collection, mixed thoroughly and stored frozen at −20 °C. Urine was collected into bottles containing sodium citrate buffer 0.5 mol litre^{-1} from an indwelling urinary catheter for 10 h after administration of cisatracurium to estimate renal excretion of cisatracurium.

Plasma and urine concentrations of cisatracurium, laudanosine and the monoquaternary alcohol metabolite (MQA) were quantified by high-performance liquid chromatography with fluorescence detection. The lower limit of quantitation was 10 ng ml^{-1} for each compound. The coefficients of variation for cisatracurium were < 14 % at concentrations between 10 and 2000 ng ml^{-1}. The coefficients of variation for laudanosine and MQA were < 9 % and < 13 %, respectively, at concentrations between 15 and 750 ng ml^{-1} for both analytes. The presence of the monoquaternary acid metabolite was assessed qualitatively by examination of the chromatograms.

Plasma concentrations of cisatracurium and its metabolites were used to construct plasma concentration–time profiles for each patient. Pharmacokinetic analysis was performed using non-compartmental methods to determine area under the concentration–time curve (AUC), plasma clearance (*Cl*), volume of distribution at steady state (V^{ss}), and elimination of half-life ($T_{\frac{1}{2}}$) of cisatracurium. The maximum concentration (C_P max), AUC, $T_{\frac{1}{2}}$ and the ratio of the metabolite AUC to cisatracurium AUC were calculated for the laudanosine and MQA metabolites.

Urine concentration data were used to calculate the total amount of cisatracurium excreted unchanged, amount of metabolites in urine and renal clearance of cisatracurium, laudanosine and MQA.

Plasma cisatracurium concentration and percentage T1 suppression data were analysed using semi-parametric effect-compartment analysis [10] to estimate concentrations in the effect compartment (site of action) and the rate constant (k_{eo}) describing the rate of equilibration between plasma concentration and neuromuscular block. The effect-compartment concentration required to produce 50% T1 suppression (EC_{50}), which is an index of patient sensitivity, and the variable (γ) describing the steepness of the effect-compartment concentration *vs* %T1 suppression curve was calculated using the sigmoid Emax model [11].

In addition, each patient was observed for adverse reactions before (baseline), during and after the treatment phases of the study. In particular, arterial pressure and airway pressures were observed closely to detect evidence of clinically significant histamine release.

One-way analysis of variance was performed to evaluate differences in the calculated variables between the two groups. Statistical significance was assumed at $P < 0.05$. Values are expressed as mean (SD).

Results

Two patients from the liver transplant group were excluded from the pharmacodynamic analysis because they received clindamycin, which may potentiate the effects of neuromuscular blocking agents. Another three patients were excluded in the liver transplant group for determination of EC_{50} because of insufficient data to accurately define EC_{50}. There was no difference in EC_{50} or the degree of maximum neuromuscular block after cisatracurium 0.1 mg kg^{-1} between the two groups (table 2). Time to maximum block was shorter in the liver transplant patients, but the clinical effective duration of action (time for T1:T0 to reach 25%), times for T1:T0 to reach 5%, 75%, and 95%, recovery indices (time for T1:T0 to recover from 25% to 75% and from 5% to 95%), and time to T4:T1 ≥ 70% were similar (table 2). There were no significant differences between the two groups in the rate constant (k_{eo}) describing the rate of equilibration between plasma concentration and neuromuscular block or in the variable (γ) describing the steepness of the effect-compartment concentration compared with the %T1 suppression curve (table 2).

Table 2 Pharmacodynamic variables for cisatracurium ($2 \times ED_{95}$) in liver transplant and control patients (mean (SD)). EC_{50} = Effect-compartment concentration resulting in 50% neuromuscular block ($n = 9$ in liver transplant group); k_{eo} = rate constant describing the rate of equilibration between plasma concentration and neuromuscular block; γ = variable describing the steepness of the effect-compartment concentration *vs* %T1 suppression curve. $^1n = 13$; $^2n = 11$; $^3n = 8$; $^4n = 10$; $^5n = 7$; $^6n = 6$; $^7n = 9$. $*P < 0.05$ compared with liver transplant patients

	Liver transplant patients ($n = 12$)	Control patients ($n = 11$)
Maximum block (%)	99.5 (1.4)^1	99.8 (0.6)
Time to maximum block (min)	2.4 (0.8)^1	3.3 (1.0)*
5% T1:T0 (min)	42.7 (10.9)	38.5 (6.1)
25% T1:T0 (min)	53.5 (11.9)^2	46.9 (6.9)
75% T1:T0 (min)	66.5 (12.3)^3	59.2 (7.6)^4
95% T1:T0 (min)	76.9 (10.0)^5	71.1 (6.7)^4
25–75% T1:T0 (min)	15.4 (4.2)^3	12.8 (1.9)^4
5–95% T1:T0 (min)	35.3 (7.5)^5	31.3 (5.1)^4
T4:T1 ≥ 70% (min)	79.0 (14.9)^6	80.4 (8.7)^4
k_{eo}	0.145 (0.029)^7	0.179 (0.079)
EC_{50} (ng ml^{-1})	79 (33)^7	98 (34)
γ	4.7 (1.9)^7	4.0 (1.6)

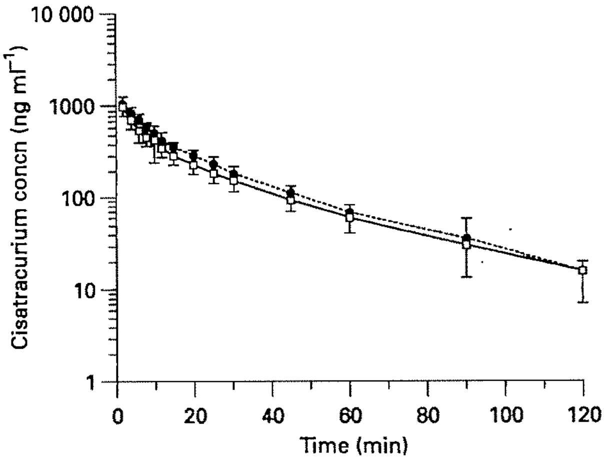


Figure 1 Semi-logarithmic plasma concentration curve of cisatracurium 0.1 mg kg^{-1} ($2 \times ED_{95}$) in liver transplant (□) ($n = 14$) and control (●) ($n = 11$) patients (mean, SD).

Table 3 Pharmacokinetic variables for cisatracurium ($2 \times ED_{95}$) in liver transplant and control patients (mean (SD)). AUC = Area under the curve; *Cl* = clearance; V^{ss} = volume of distribution at steady state; $T_{\frac{1}{2}}$ = elimination half-life. $^1n = 12$. $*P < 0.05$ compared with liver transplant patients

	Liver transplant patients ($n = 13$)	Control patients ($n = 11$)
AUC (μg min ml^{-1})	16.6 (3.2)	19.1 (2.9)*
Cl (ml min^{-1} kg^{-1})	6.6 (1.1)	5.7 (0.8)*
V^{ss} (ml kg^{-1})	195 (38)	161 (23)*
$T_{\frac{1}{2}}$ (min)	24.4 (2.9)^1	23.5 (3.5)

One patient in the liver transplant group did not have complete blood sampling and was eliminated from the pharmacokinetic analysis. Plasma cisatracurium concentration *vs* time data were similar in the two groups (fig. 1). The pharmacokinetic variables of cisatracurium are shown in table 3. Patients with liver disease had a higher clearance and larger volume of distribution at steady state than control patients. However, elimination half-life was similar in both groups. There was no or a poor correlation between albumin concentrations and *Cl* or V^{ss}.

The percentage of cisatracurium recovered unchanged from the urine was 11.4 (6.6)% in 11 liver transplant patients and 14.3 (4.0)% in eight control patients. Renal clearance of cisatracurium was 0.62 (0.32) ml min^{-1} kg^{-1} in liver transplant patients ($n = 10$) and 0.80 (0.26) ml min^{-1} kg^{-1} in control patients ($n = 8$).

Maximum plasma laudanosine concentrations were 16 (5) ng ml^{-1} and 21 (5) ng ml^{-1} in liver transplant and control patients, respectively. Maximum plasma MQA concentrations were 73 (14) ng ml^{-1} and 82 (12) ng ml^{-1}, respectively. Monoquaternary acid was not detected on any chromatogram from any plasma or urine sample.

The $T_{\frac{1}{2}}$ of laudanosine was determined in only two liver transplant and four control patients. In the other patients, plasma concentrations were less than the detection limit or there were less than three quantifiable concentration–time points in the terminal phase. The laudanosine $T_{\frac{1}{2}}$ values in liver transplant patients were 7.2 and 8.2 h, and in control patients the $T_{\frac{1}{2}}$ ranged from 1.6 to 4 h. The $T_{\frac{1}{2}}$ of MQA was 61.9 (9.4) and 39.8 (9.9) min for 11 liver transplant and seven control patients, respectively.

The mean amount of laudanosine excreted in the 10-h urine collection period was 602 (280) µg in 11 liver transplant patients and 503 (260) µg in eight control patients. Renal clearance of laudanosine was 0.6–1.2 ml min^{-1} kg^{-1} in two evaluable liver transplant patients. Renal clearance of laudanosine was 1.35 (0.89) ml min^{-1} kg^{-1} in four control patients.

Mean amount of MQA in urine were 449 (213) and 391 (139) µg in 11 liver transplant and eight control patients, respectively. Renal clearance of MQA was 0.59 (0.33) and 0.90 (0.39) ml min^{-1} kg^{-1} in liver transplant ($n = 8$) and control ($n = 6$) patients, respectively.

There were no clinically significant changes in arterial pressure, heart rate or airway pressure after administration of cisatracurium, and no other untoward effects were noted in any patient after bolus administration of cisatracurium.

Discussion

The pharmacokinetics and pharmacodynamics of cisatracurium were determined in liver transplant and control patients. Cisatracurium is eliminated from the body via Hofmann elimination in the central (plasma) and peripheral (tissue) compartments; elimination from the peripheral compartment cannot be estimated *in vivo*. Therefore, non-compartmental, rather than compartmental, methods were used to calculate pharmacokinetic variables. Non-compartmental methods are based on the assumption that elimination occurs only from the central compartment. *Cl*, an exit-site independent variable, is similar whether or not it is determined using compartmental or non-compartmental methods. V^{ss}, however, is underestimated when elimination from the peripheral compartment is ignored (i.e. when non-compartmental methods are used) [12].

We found that the pharmacokinetic variables (*Cl*, $T_{\frac{1}{2}}$ and V^{ss}) of cisatracurium in our control patients were similar to those observed in other studies of cisatracurium [3, 13]. In addition, these variables (*Cl*, $T_{\frac{1}{2}}$ and V^{ss}) in our control patients were similar to those of atracurium in healthy patients [8, 14–17]. The presence of liver disease changed the pharmacokinetics of cisatracurium to a limited degree: V^{ss} of cisatracurium was approximately 20% larger and mean plasma clearance was approximately 16% greater in liver transplant patients than in control patients, although $T_{\frac{1}{2}}$ was not different. Similar findings have been reported for atracurium in patients with liver disease [8, 14–16]. Because a chemical degradation process (Hofmann elimination) is the major elimination pathway for cisatracurium [9], the higher clearance in liver transplant patients is most likely explained by the larger volume of distribution rather than a change in organ clearance.

The clinical effective duration of action (time for T1:T0 to reach 25%) in our control patients was similar to that observed in other studies of cisatracurium [1, 2]. Recovery indices (time for T1:T0 to recover from 25% to 75% and from 5% to 95%) in our control patients were similar to those observed by Belmont and colleagues [1] but were shorter than those observed by Boyd and colleagues [2]. The time to maximum block in our control patients was shorter than that found in other studies of cisatracurium [1–4]. Furthermore, the time to onset for cisatracurium was shorter in liver transplant than in control patients, although the duration of action was similar in both groups. These findings are in contrast with results reported for atracurium: the time to onset of action was longer and the duration of action shorter for atracurium in patients with hepatic dysfunction [18]. It is possible that our patients had more severe liver disease than those studied by Bell and co-workers, as most of their patients had only mild liver disease [18]. Therefore, our patients may have had a more hyperdynamic circulation with higher perfusion of muscles, resulting in a shorter time to onset. A slightly lower EC_{50} (although not statistically significant) in our patients with liver disease may have contributed to this observation.

Plasma laudanosine and MQA concentrations after cisatracurium 0.1 mg kg^{-1} were much lower than those observed after administration of atracurium besylate 0.3 mg kg^{-1} [8]; this dose of atracurium besylate is less potent than the dose of cisatracurium we used. Although cisatracurium is approximately three times more potent than atracurium expressed in terms of its cation, the dose of atracurium is expressed as its besylate salt, whereas that of cisatracurium is not, indicating that 0.1 mg kg^{-1} of cisatracurium is equipotent to approximately 0.5 mg kg^{-1} of atracurium besylate. Peak laudanosine concentrations after atracurium were 180 (80) and 190 (40) ng ml^{-1} in patients with liver disease and in normal patients, respectively [8]. Similar laudanosine concentrations were observed in another study [16]. However, after cisatracurium, peak laudanosine concentrations were 16 (5) and 21 (5) ng ml^{-1} in liver transplant and control patients, respectively. Similarly, peak MQA concentrations after atracurium were as high as 480 (180) and 490 (70) ng ml^{-1} in patients with liver disease and in normal patients, respectively [8] while after cisatracurium, peak MQA concentrations were 73 (14) and 82 (12) ng ml^{-1}, respectively. These differences may be related, at least in part, to the higher potency of cisatracurium, resulting in less substrate for metabolization.

The number of patients with evaluable $T_{\frac{1}{2}}$ data for laudanosine was small and therefore no conclusions can be drawn on the effect of liver disease on the elimination characteristics of laudanosine. Nevertheless, the pharmacokinetics of laudanosine and MQA after cisatracurium in both patients with liver disease and controls were similar to those reported after atracurium [8, 16]. The $T_{\frac{1}{2}}$ of laudanosine was also longer in patients with liver disease after atracurium administration [8, 16, 19], indicating that the liver plays an important role in the clearance of laudanosine. Similar observations have been made for MQA [8]. Because of the altered pharmacokinetics of these metabolites in patients with liver disease, cisatracurium may be the preferred drug compared with atracurium because of the significantly lower plasma concentrations of laudanosine and MQA after equipotent doses of these neuromuscular blocking agents.

Liver disease does not appear to have an effect on the urinary excretion of cisatracurium. Similar findings have been published for atracurium [19]. In fact, renal clearance and renal elimination of unchanged drug may be slightly greater for cisatracurium than for atracurium [17, 19, 20]. This may be related to the fact that atracurium contains short-acting isomers that are less likely to appear in the urine.

Acknowledgement

Cisatracurium was provided by Glaxo Wellcome, who also supported the study financially. We thank Karen Latta for the expert technical assistance and Cindy Rawls for analytical support.

References

1. Belmont MR, Lien CA, Quessy S, Abou-Donia MM, Abalos A, Eppich L, Savarese JJ. The clinical neuromuscular pharmacology of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. *Anesthesiology* 1995; **82**: 1139–1145.
2. Boyd AH, Eastwood NB, Parker CJR, Hunter JM. Pharmacodynamics of the 1R *cis*-1′R *cis* isomer of atracurium (51W89) in health and chronic renal failure. *British Journal of Anaesthesia* 1995; 74: 400–404.
3. Ornstein E, Lien C, Matteo RS, Ostapkovich N, Wolf K, Kisor D, Diaz J. Pharmacodynamics and pharmacokinetics of 51W89 in geriatric surgical patients. *Anesthesiology* 1994; **81**: A1076.
4. Lepage JY, Malinovsky JM, Malinge M, Cozian A, Pinaud M. Comparison of equipotent doses of 51W89 and atracurium. *Anesthesiology* 1994; **81**: A1090.
5. Lien CA, Belmont MR, Abalos A, Eppich L, Quessy S, Abou-Donia MM, Savarese JJ. The cardiovascular effects and histamine-releasing properties of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anesthesia. *Anesthesiology* 1995; **82**: 1131–1138.
6. Welch RM, Brown A, Ravitch J, Dahl R. The in vitro degradation of cisatracurium, the *R, cis-R′*-isomer of atracurium, in human and rat plasma. *Clinical Pharmacology and Therapeutics* 1995; **58**: 132–142.
7. Stiller RL, Cook DR, Chakravorti S. *In vitro* degradation of atracurium in human plasma. *British Journal of Anaesthesia* 1985; 57: 1085–1088.
8. Ward S, Weatherley BC. Pharmacokinetics of atracurium and its metabolites. *British Journal of Anaesthesia* 1986; **58**: 6S–10S.
9. Kisor DF, Wargin WA, Schmith VD, Cook DR, Ornstein E. Organ-independent Hofmann elimination is the major clearance pathway of the neuromuscular blocking agent 51W89 in man. *Pharmaceutical Research* 1994; **11**: S335.
10. Verotta D, Sheiner LB. Simultaneous modeling of pharmacokinetics and pharmacodynamics: an improved algorithm. *Computer Applications in the Biosciences* 1987; **3**: 345–349.
11. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J. Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to *d*-tubocurarine. *Clinical Pharmacology and Therapeutics* 1979; **25**: 358–371.
12. Nakashima E, Benet LZ. General treatment of mean residence time, clearance, and volume parameters in linear mamillary models with elimination from any compartment. *Journal of Pharmacokinetics and Biopharmaceutics* 1988; **16**: 475–492.
13. Lien CA, Schmith VD, Belmont MR, Kisor D, Savarese JJ. Pharmacokinetics/dynamics of 51W89 in healthy patients during opioid anesthesia. *Anesthesiology* 1994; **81**: A1082.
14. Ward S, Neill EAM. Pharmacokinetics of atracurium in acute hepatic failure (with acute renal failure). *British Journal of Anaesthesia* 1983; **55**: 1169–1172.
15. Cook DR, Brandom BW, Stiller RL, Woelfel S, Lai A, Slater J. Pharmacokinetics of atracurium in normal and liver failure patients. *Anesthesiology* 1984; **61**: A433.
16. Parker CJR, Hunter JM. Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis. *British Journal of Anaesthesia* 1989; **62**: 177–183.
17. Shearer ES, O'Sullivan EP, Hunter JM. Clearance of atracurium and laudanosine in the urine and by continuous venovenous haemofiltration. *British Journal of Anaesthesia* 1991; **67**: 569–573.
18. Bell CF, Hunter JM, Jones RS, Utting JE. Use of atracurium and vecuronium in patients with oesophageal varices. *British Journal of Anaesthesia* 1985; **57**: 160–168.
19. Bion JF, Bowden MI, Chow B, Honisberger L, Weatherley BC. Atracurium infusions in patients with fulminant hepatic failure awaiting liver transplantation. *Intensive Care Medicine* 1993; **19** (Suppl. 2): S94–S98.
20. Vandenbrom RHG, Wierda JMKH, Agoston S. Pharmacokinetics and neuromuscular blocking effects of atracurium besylate and two of its metabolites in patients with normal and impaired renal function. *Clinical Pharmacokinetics* 1990; **19**: 230–240.

British Journal of Anaesthesia 1996; **76**: 629–631

Soluble E-cadherin concentrations in patients with systemic inflammatory response syndrome and multiorgan dysfunction syndrome

A. J. PITTARD, R. E. BANKS, H. F. GALLEY AND N. R. WEBSTER

Summary

We have assessed the role of the cell–cell adhesion molecule, E-cadherin, in the pathogenesis of multiorgan failure in 24 intensive care patients with sepsis and varying degrees of organ dysfunction, compared with 21 healthy subjects. Plasma soluble E-cadherin (sE-cadherin) was measured by enzyme immunoassay. The median concentration of sE-cadherin in normal subjects was 3.21 μg ml^{-1} compared with 6.00 μg ml^{-1} in patients with sepsis and organ dysfunction ($P = 0.0019$). There was no statistically significant difference in concentrations of sE-cadherin in survivors compared with non-survivors. Concentrations of sE-cadherin tended to increase with the severity of organ failure. We conclude that sE-cadherin is increased in inflammation and injury, and may be related to the degree of multiorgan failure after sepsis. (*Br. J. Anaesth.* 1996; **76**: 629–631)

Key words

Complications: multiple organ dysfunction syndrome. Complications, septicemia. Pharmacology, cadherin.

Sepsis, septic shock and multiorgan failure are important contributors to mortality and morbidity in patients in the intensive care unit [1–3]. Shock and infection are the two most common predisposing factors in the development of multiorgan dysfunction [3], causing an inflammatory response initiating a cascade of events leading to widespread endothelial damage [2, 4, 5] and failure of the microcirculation. Adhesion molecules are important in cell–cell and cell–matrix interactions. Integrins and selectins play fundamental roles in the interaction between leucocytes and endothelial cells [6, 7]. Cadherins mediate cell–cell adhesion and are important in maintaining tissue architecture and consequently organ function. E-cadherin is a cell adhesive molecule found in a variety of tissues [8]. Soluble forms of integrins, selectins and cadherins have been identified.

Increased concentrations of immunoreactive soluble forms of endothelial adhesion molecules have been found in patients with sepsis and multiorgan dysfunction [9–11]. Increased concentrations of soluble E-cadherin (sE-cadherin) have been reported in patients with various cancers [8, 12]. There has been no previous study on the role of E-cadherin in patients with sepsis. Circulating sE-cadherin may reflect tissue turnover or regeneration, and may be important in the regulation of normal organ function. We have measured plasma sE-cadherin concentrations in patients with sepsis and varying degrees of multiorgan dysfunction.

Patients and methods

After approval by the local Clinical Research Ethics Committee, we studied 24 consecutive patients admitted to the intensive care unit, who were more than 18 yr of age, when they fulfilled the Bone sepsis criteria [13]. Fourteen patients were medical patients, nine were postoperative and one was post-trauma. Blood samples were obtained from an indwelling arterial cannula and collected into a heparinized tube. APACHE II score and numbers of dysfunctioning organs (table 1) [14] were recorded at sampling. In four patients sequential samples were obtained when patients developed increasing numbers of dysfunctional organs. After immediate centrifugation, plasma was separated into aliquots and stored at −20 °C for assay of sE-cadherin. Venous blood samples were also obtained from 21 healthy subjects (11 male) aged 21–54 yr.

Samples were assayed for sE-cadherin using a commercially available sandwich enzyme immunoassay (Takara Shuzo Co. Ltd, Japan). Briefly, a microtitre plate was coated with a mouse monoclonal anti-human E-cadherin antibody, non-specific binding was blocked using a blocking buffer and diluted samples and standards were added to the wells. After incubation and washing steps, an anti-mouse IgG antibody conjugated with horseradish peroxidase was then added to each well, incubated, washed and bound sE-cadherin detected by incubation with substrate (*o*-phenylenediamine). After the addition of stop solution, the absorbances of the wells were measured at 490 nm using a Titertek Multiskan MCC reader and the concentration of sE-cadherin determined by comparison with the standard curve

---

A. J. PITTARD, FRCA, H. F. GALLEY*, PHD, FIMLS, N. R. WEBSTER*, PHD, FRCA (Department of Anaesthesia); R. E. BANKS, PHD (ICRF Institute of Cancer Medicine Research); St James's University Hospital Trust, Leeds LS9 7TF. Accepted for publication: December 12, 1995.

* Present address:

Anaesthesia and Intensive Care, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen AB9 2ZD.

Correspondence to N.R.W.

Table 1 Definitions of organ dysfunction [14]

Organ system	Definition
Cardiovascular	Systolic AP < 90 mm Hg or requiring vasopressors
Respiratory	Ventilatory frequency < 5 or > 20 bpm, requiring mechanical ventilation, or Pa_{O_2}/FI_{O_2} < 36.8 kPa
Renal	Creatinine > 280 mmol litre^{-1}
Hepatic	Bilirubin > 51 mmol litre^{-1}
Haematological	Platelet count < 100 × 10^9 litre^{-1}
Neurological	Glasgow coma scale < 8 (in the absence of sedation)
Gastrointestinal	Stress ulcer requiring > 2 u. transfusion

using Flexicalc software (Wallac, Finland). All standards and samples were assayed in duplicate. The coefficient of variation (CV) of replicate samples was less than 10 % and a between-plate CV based on a sample with a mean value of 3.3 µg ml^{-1} was 13.1 % ($n = 4$).

Data were analysed using Microsoft Excel 5.0 with Astute statistical software add-in. When tested for normality using the Komolgorov–Smirnov goodness-of-fit test and normal plots, the data were found to be non-normally distributed and accordingly non-parametric statistical tests were used. Comparison of sE-cadherin concentrations at study entry between survivors and non-survivors, and healthy subjects was made using the Mann–Whitmey *U* test. Pearson rank linear regression was used to assess the relationship between APACHE II score and sE-cadherin concentrations. Kruskal–Wallis ANOVA was used to assess the relationship between sE-cadherin concentrations and the degree of organ failure. $P < 0.05$ was considered statistically significant.

Results

We studied 24 patients, median age 65 (range 19–79) yr, 18 of whom were male. The median APACHE II score at the time of sampling was 26 (13–39). Sixteen patients died (67 %). The median APACHE score in those who died was 25.5 (16–37) and 20.5 (13–31) in survivors (ns). Immunoreactive sE-cadherin concentrations were significantly higher in patients with sepsis and organ dysfunction (6.00 (0.98–19.98) µg ml^{-1}) than those in healthy subjects (3.28 (1.18–6.88) µg ml^{-1}) ($P = 0.0019$) (fig. 1). There was a tendency for sE-cadherin concentrations to increase with the degree of organ dysfunction, although this failed to reach statistical significance (fig. 2). There was no difference in sE-cadherin concentrations between patients who died (5.53 (2.10–19.98) µg ml^{-1}) and those who survived (8.63 (0.98–11.98) µg ml^{-1}) ($P = 0.86$). sE-cadherin concentration did not correlate with APACHE II score ($r = -0.25$, $P = 0.25$).

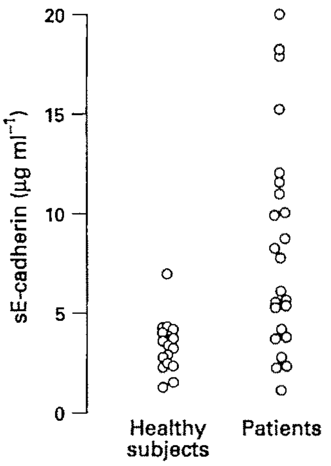


Figure 1 Plasma soluble E-cadherin (sE-cadherin) concentrations in healthy subjects compared with samples obtained at study entry in intensive care patients with sepsis and organ failure ($P = 0.0019$, Mann–Whitmey *U* test).

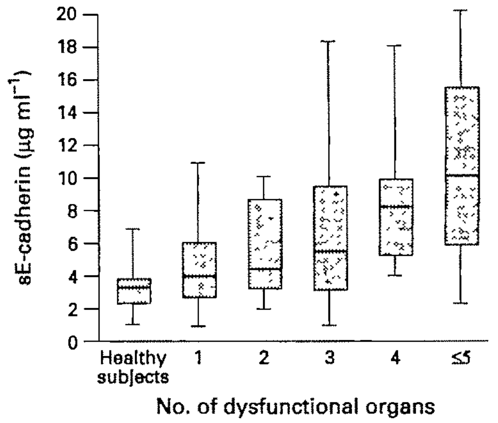


Figure 2 Plasma soluble E-cadherin (sE-cadherin) concentrations in 21 healthy subjects and 24 patients with increasing degrees of organ failure. The box and whisker plots represent median with 25 and 75 percentile concentrations; maximum and minimum concentrations are shown as bars ($P = 0.51$, Kruskal–Wallis ANOVA in patients).

Discussion

We have demonstrated significantly increased concentrations of the cell–cell and cell–matrix adhesion molecule, soluble E-cadherin, in patients with sepsis and organ dysfunction. Plasma concentrations tended to correlate with increasing severity of illness, as reflected by the increasing numbers of organ systems failing. It is possible that these increased concentrations reflect the severity of tissue damage and degree of epithelial turnover and may suggest a role for abnormalities in intercellular adhesion in the pathogenesis of multiorgan dysfunction and failure.

Cadherins play an essential role in normal growth and tissue development. There have been three forms described, E-, N- and P-, with characteristic tissue distribution [8]. They share a common primary structure and all mediate cell–cell adhesion and maintenance of normal tissue architecture. Several studies have shown that loss of cell surface immunoreactive E-cadherin is associated with tumour progression and tissue invasion [8, 12]. Soluble forms of E-cadherin have been identified in plasma representing functionally active degradation fragments and may indicate either regeneration or loss of cell surface E-cadherin.

We suggest that increased sE-cadherin concentrations represent increased cleavage of tissue E-cadherin secondary to increased protease activity [15] or free radical release [14] from activated neutrophils resulting in loss of tissue architecture and function. However, it is possible that there is a generalized increase in epithelial cell turnover with an associated requirement for E-cadherin regeneration. *In vitro*, interleukin-1 causes shedding of biologically active E-selectin (an endothelial cell adhesion molecule) from the cell surface of cultured human endothelial cells [10]. It is not clear if cytokines present in the circulation of septic patients as a result of the inflammatory process can cause similar shedding of other adhesion molecules.

In the present study, measured immunoreactive sE-cadherin concentrations may have been underestimated as high concentrations of proteolytic enzymes may have yielded smaller fragments which may not have been detected in the assay system used. However, concentrations in our patients with sepsis were generally higher than those reported previously with various tumours [12]. Moreover, marked differences were found between plasma from patients with sepsis and that from healthy subjects.

In summary, we have shown increased circulating concentrations of sE-cadherin in patients with sepsis and varying degrees of multiple organ failure. Further studies are required to elucidate the mechanism of shedding and the pathophysiological role of E-cadherin in such patients.

Acknowledgement

We gratefully acknowledge the gift of soluble E-cadherin enzyme immunoassay kits from Takara Shuzo Co. Ltd.

References

1. Cunnion RE, Parillo JE. Myocardial function in sepsis. Recent insights. *Chest* 1989; **95**: 941–945.
2. Parker MM, Parillo JE. Septic shock: Hemodynamics and pathogenesis. *Journal of the American Medical Association* 1983; **250**: 3324–3327.
3. Rello J, Ricart M, Mirelis B, Quintana E, Gurgui M, Net A, Prats G. Nosocomial bacteraemia in a medical-surgical intensive care unit: epidemiological characteristics and factors influencing mortality in 111 episodes. *Intensive Care Medicine* 1994; **20**: 94–98.
4. Bone RC. The pathogenesis of sepsis. *Annals of Internal Medicine* 1991; **115**: 457–469.
5. Glauser MP, Zanetti G, Baumgartner JD, Cohen J. Septic shock: pathogenesis. *Lancet* 1991; **338**: 732–736.
6. Cronstein BN, Weissmann G. The adhesion molecules of inflammation. *Arthritis and Rheumatism* 1993; **36**: 147–157.
7. Bevilacqua MP, Nelson RM. Endothelial–leucocyte adhesion molecules in inflammation and metastases. *Thrombosis and Haemostasis* 1993; **70**: 152–154.
8. Takeichi M. Cadherins in cancer: implications for invasion and metastasis. *Current Opinions in Cell Biology* 1993; **5**: 806–811.
9. Redl H, Dinges HP, Buurman WA. Expression of endothelial leukocyte adhesion molecule 1 in septic but not traumatic/hypovolemic shock in the baboon. *American Journal of Pathology* 1991; **139**: 461–466.
10. Newman W, Dawson Beall L, Carson CW, Hunder GG, Graben N, Randhawa ZI, Gopal TV, Wiener-Kronish J, Matthay MA. Soluble E-selectin is found in supernatants of activated endothelial cells and is elevated in the serum of patients with septic shock. *Journal of Immunology* 1993; **150**: 644–654.
11. Cowley HC, Heney D, Gearing AJ, Hemingway I, Webster NR. Increased circulating adhesion molecule concentrations in patients with the systemic inflammatory response syndrome: a prospective cohort study. *Critical Care Medicine* 1994; **22**: 651–657.
12. Katayama M, Hirai S, Kamihagi K, Nakagawa K, Yasumoto M, Kato I. Soluble E cadherin fragments increase in the circulation of cancer patients. *British Journal of Cancer* 1994; **69**: 580–585.
13. Bone RC. Definitions for sepsis and organ failure and guidelines for innovative therapies in sepsis. *Chest* 1993; **101**: 1644–1655.
14. Goode HF, Cowley HC, Walker BE, Howdle PD, Webster NR. Decreased antioxidant status and increased lipid peroxidation in patients with septic shock and secondary organ dysfunction. *Critical Care Medicine* 1995; **23**: 646–651.
15. Barron RL. Pathophysiology of septic shock and implications for therapy. *Clinical Pharmacy* 1993; **12**: 829–845.

British Journal of Anaesthesia 1996; **76**: 632–639

Preoperative inhibition of angiotensin-converting enzyme improves systemic and renal haemodynamic changes during aortic abdominal surgery

M. LICKER, M. BEDNARKIEWICZ, P. NEIDHART, R. PRÊTRE, M. MONTESSUIT, H. FAVRE AND D. R. MOREL

Summary

We studied 22 patients undergoing aortic surgery, allocated randomly to receive, before induction of anaesthesia, a single i.v. dose of enalapril 50 μg kg^{-1} or saline. During infrarenal aortic cross-clamping, we observed similar reductions in oxygen uptake in the two groups, despite greater systemic oxygen delivery in enalapril-treated patients; angiotensin-converting enzyme inhibition prevented the reduction in cardiac output and attenuated the decrease in glomerular filtration. Changes in glomerular filtration secondary to aortic clamping were related positively to changes in renal plasma flow ($r = 0.83$ (saline group) and $r = 0.65$ (enalapril group)). Creatinine clearance on the first day after operation was significantly higher in the enalapril compared with the saline group. We conclude that enalapril pretreatment is effective in improving systemic oxygen delivery, renal plasma flow and glomerular filtration during aortic abdominal surgery. (*Br. J. Anaesth.* 1996; **76**: 632–639)

Key words

Surgery, vascular. Kidney, blood flow. Kidney, function. Pharmacology, ACE inhibitors.

Major haemodynamic disturbances are often encountered during aortic abdominal surgery. In most instances, infrarenal aortic cross-clamping causes decreases in cardiac output, oxygen delivery and oxygen uptake that are associated with reduced renal blood flow and glomerular filtration rate [1]. After release of the aortic clamp, systemic haemodynamic and metabolic changes revert rapidly to normal, whereas renal function remains impaired, at least temporarily [2].

Although the mechanisms of perioperative renal insufficiency were believed to be related to relative hypovolaemia, decreased myocardial function and increased sympathetic nervous activity, neither fluid volume expansion nor sympathetic block, nor the use of mannitol or dopamine have been shown to attenuate these perioperative changes consistently [3, 4]. Powerful endogenous vasoconstricting substances such as thromboxane A_2, oxygen-derived free radicals and endothelin-1 have been shown to be released during aortic clamping, and all might contribute to prolonged impairment of renal function [5–7]. The importance of the renin–angiotensin system (RAS) has also been emphasized in the regulation of arterial pressure, blood flow distribution and renal function [8]. Experimental evidence suggests that angiotensin II mediates widespread vasoconstriction by causing direct activation of transmembrane calcium transport and indirectly facilitating release of noradrenaline, by sensitizing adrenergic receptors, and also by enhancing the synthesis of thromboxane and endothelin-1 [9]. Clinical investigations have reported increased plasma renin activity (PRA) and angiotensin II concentrations during major surgical procedures, including aortobifemoral bypass [10, 11], suggesting that angiotensin II may account to some extent for perioperative circulatory and renal haemodynamic impairment.

Recently, angiotensin-converting enzyme inhibitors (ACEI) have been prescribed successfully for the treatment of hypertension and congestive heart failure [12]. In addition to normalizing elevated arterial pressure, ACEI treatment improves cardiac output by lowering vascular resistances and also produces renal vasodilatation and natriuresis. Interestingly, these agents have been advocated to prevent deterioration of renal function in hypertensive and diabetic patients [13]. Based on these beneficial effects, and as the RAS is known to be stimulated during aortic abdominal surgery, we hypothesized that ACE inhibition would potentially attenuate systemic haemodynamic and renal functional impairments. Therefore, we tested, in a double-blind randomized study, if a single dose of ACEI administered before operation would preserve systemic oxygen delivery and provide protective renal effects in adult patients undergoing infrarenal aortic surgery.

MARC LICKER, MD, PETER NEIDHART, MD (Division of Anaesthesiology); MAREK BEDNARKIEWICZ, MD, RENÉ PRÊTRE, MD, MICHEL MONTESSUIT, MD (Clinics of Cardiovascular Surgery); HERVÉ FAVRE, MD (Division of Nephrology); DENIS R. MOREL*, MD (Division of Anaesthesiological Investigations); University Hospital of Geneva, CH-1211 Geneva 14, Switzerland. Accepted for publication: January 1, 1996.

*Address for correspondence: Division d'Investigations Anesthésiologiques, Hôpital Cantonal Universitaire, CH-1211 Genève 14, Switzerland.

Patients and methods

We studied 22 patients undergoing elective infrarenal aortic surgery because of aortic aneurysm or atherosclerotic occlusive disease. Informed consent was obtained and the study was approved by the Committee for Ethics in Clinical Research of our institution. Patients with preoperative renal dysfunction (creatinine clearance < 50 ml min^{-1} 1.73 m^{-2}), cardiac insufficiency (episodes of congestive heart failure or left ventricular ejection fraction $< 40\%$), myocardial infarction within the last 6 months, renal artery stenosis detected on the angiogram or those receiving ACEI therapy were excluded.

Usual cardiac medications, except diuretics, were continued up to and including the morning of surgery. Patients were premedicated with midazolam 7.5 mg orally and morphine 0.1 mg kg^{-1} i.m. In the induction room, radial and thermodilution pulmonary arterial catheters were inserted during local anaesthesia for measurement of mean arterial (MAP), central venous (CVP) and pulmonary capillary wedge pressures (PCWP), and intermittent cardiac output (CO) determination. Electrocardiographic leads II and V5 were attached for monitoring heart rate (HR) and ST changes.

Anaesthesia was induced with alfentanil 30–40 µg kg^{-1} i.v., given over 1–2 min, followed by thiopentone to loss of the eyelid reflex (3–5 mg kg^{-1}). Neuromuscular block was achieved with pancuronium 0.1 mg kg^{-1}. After tracheal intubation, mechanical ventilation with an air–oxygen mixture was adjusted to maintain arterial blood-gas tensions within the normal range (end-expiratory carbon dioxide fraction 4–4.5% and arterial oxygen saturation greater than 94%). A Foley urinary bladder catheter was inserted after induction of anaesthesia for urinary sampling and urine flow measurement. Throughout the surgical procedure, anaesthesia was maintained with an i.v. infusion of alfentanil 80–120 µg kg^{-1} min^{-1} supplemented with inhaled isoflurane (up to 2%). Phenylephrine was administered at the discretion of the anaesthetist in order to maintain MAP within a clinically acceptable range (20% of preoperative values).

Before operation, crystalloids 12 ml kg^{-1} (containing Na$^+$ 130 mmol litre^{-1}, Cl$^-$ 118 mmol litre^{-1} and K$^+$ 5.4 mmol litre^{-1}) were infused over 20 min in all patients. During surgery, fluid loading was titrated to maintain PCWP at 10–15 mm Hg. Red blood cell concentrates were given when packed cell volume (PCV) decreased to less than 25%. A blood salvage device (Cell Saver 4; Haemonetics Braintree, MA, USA) was used in each case to reduce the need for homologous blood transfusion.

Patients were allocated in a randomized, double-blind manner to one of two groups: the enalapril group received enalapril 50 µg kg^{-1} (Reniten, Merck, Sharp & Dohme Research Laboratories, NJ, USA) diluted in 20 ml of normal saline and injected i.v. over 5 min ($n = 12$); the saline group received the same volume of saline solution ($n = 10$). In a dose-finding study, conducted in similar surgical patients, we demonstrated that a single 50-µg kg^{-1} i.v. injection given before surgery produced marked inhibition ($> 90\%$) of plasma angiotensin-converting enzyme activity for more than 20 h whereas lower doses (10 and 30 µg kg^{-1}) produced ACE inhibition of shorter duration (90% ACE inhibition up to 4 and 8 h after administration of enalapril 10 and 30 µg kg^{-1}, respectively). The drugs were given 25 min before induction of anaesthesia, when a stable basal systemic haemodynamic state had been reached and while patients were fluid loaded with i.v. crystalloids. The subsequent changes in haemodynamic state, oxygen uptake and renal function were assessed in the two groups before and during aortic cross-clamping and after aortic unclamping.

Blood temperature and cardiac output, determined in triplicate by injection of 10 ml of 5% glucose solution, were measured by a cardiac output computer (Model 9520A, American Edwards Laboratories, Irvine, CA, USA). Systemic haemodynamic data (HR, MAP, CVP, PCWP, CO) were recorded at end-expiration at the following times: (1) before anaesthesia (i.e. before and 20 min after administration of drug), (2) during the surgical aortic approach (i.e. 2 min after skin incision, and 2 min before aortic cross-clamping), (3) during aortic cross-clamping (i.e. 5 min after aortic cross-clamping and immediately before ilio–femoral unclamping) and (4) after vascular unclamping (i.e. 2 min after "first leg" unclamping, and during peritoneal closure). Systemic vascular resistance index (SVRI) and cardiac index (CI) were calculated according to standard formulae.

Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were estimated using a constant infusion technique of inulin and para-aminohippuric acid (PAH). Priming doses of inulin 30 mg kg^{-1} (10% Inulin; Laevosan GmbH, Linz, Austria) and PAH 8 mg kg^{-1} (Merck, Sharp & Dohme, NJ, USA) were given i.v. followed by a continuous infusion of both drugs at doses of 0.20 mg kg^{-1} min^{-1} and 0.15 mg kg^{-1} min^{-1}, respectively. After an 80-min equilibration period, urine was collected over at least 30 min before (pre-clamping) and during aortic cross-clamping (clamping), and after "first leg" reperfusion (post-clamping); arterial blood was sampled in the middle of each collection period. Urinary and plasma inulin and PAH concentrations were assayed spectrophotometrically. Inulin and PAH clearances (C_{IN}, C_{PAH}) were calculated as the respective urine concentration divided by arterial plasma concentration multiplied by urine volume in ml min^{-1}; these data were corrected for standard body surface area (1.73 m^2). As PAH handling within the kidney is altered during surgery and anaesthesia, the renal extraction fraction of PAH (E_{PAH} = arterial − venous plasma concentration divided by arterial concentration of PAH) was determined. Therefore, the surgeon directly punctured the renal vein and slowly withdrew venous blood as close to the kidney as possible. A "corrected" ERPF was obtained (ERPF = C_{PAH}/E_{PAH}) and RBF was calculated as: RBF = ERPF × 100/(100 − PCV). During the pre-clamping, aortic clamping and post-clamping periods, systemic haemodynamic variables (MAP, CVP, CO) were averaged as the mean of three measurements obtained 15 min apart at the beginning, middle and end of urine sampling. Renal vascular resistance (RVR) and fractional renal blood flow (RBF) were calculated using the following equations: RVR = (MAP − CVP)/RBF × 79.9 and fractional RBF = RBF/CO × 100.

Additional renal functional tests comprised calculation of creatinine clearance (C_{Creat}), fractional sodium excretion (FE_{Na^+}), total sodium excretion (U_{Na^+}) and protein excretion. FE_{Na^+} was calculated by dividing the urine-to-plasma sodium ratio by the urine-to-plasma creatinine ratio times 100; U_{Na^+} equals the product of urinary sodium and urinary flow. Proteinuria and C_{Creat} were also assessed on the day before surgery and 12 h after operation (12-h urine collection period). Serum and urinary sodium and creatinine concentrations were measured with a standard flame emission photometer. Diuretics, mannitol and dopamine were not given during the entire study.

In arterial and mixed venous blood samples, haemoglobin (Hb), oxygen tension and oxygen saturation (Sa_{O_2}, $S\bar{v}_{O_2}$) were measured directly (ABL Radiometer OSM3, Copenhagen, Denmark). Total body oxygen consumption ($\dot{V}O_2$) was estimated as the product of CO and the arteriovenous oxygen content difference. Total body oxygen delivery (DO_2) was derived as CO × arterial oxygen content.

STATISTICAL ANALYSIS

All data are expressed as mean (SD). The influence of enalapril treatment was tested by the Mann–Whitney two-sample test. To determine if differences existed between times, repeated measures analysis of variance was performed followed by the two-tailed paired Student's t test and Dunnett's correction for multiple comparisons. Regression analyses between changes in systemic and renal haemodynamic state and renal functional variables in response to aortic clamping and after aortic unclamping were analysed within each group. Correlations were also determined between inulin and creatinine clearance and between changes in DO_2 and $\dot{V}O_2$. For all statistical comparisons, significance was defined as $P < 0.05$.

Results

Two patients (one in each group) were excluded from the study because the surgeon had to proceed with vascular clamping involving one (or both) renal artery(ies). Therefore, there were nine and 11 patients in the saline and enalapril groups, respectively. There were no differences between the two groups in preoperative clinical characteristics and surgical management (table 1). All patients (except one in the saline group) were treated with either β-blockers, calcium-channel blockers, diuretics or a combination of these drugs. Preoperative creatinine clearance was within the normal range in both groups. Intraoperative fluid requirements tended to be slightly greater in the enalapril group compared with the saline group, but this was not statistically significant for red cell transfusion and crystalloid infusion.

SYSTEMIC HAEMODYNAMIC AND METABOLIC DATA (fig. 1, table 2)

Before anaesthesia and after fluid loading, enalapril 50 μg induced increases in CI (+12%; $P = 0.023$) and DO_2 and decreases in SVRI, without changes in MAP and HR. In the saline group, CI tended to increase, although this was not significant (+7%). General anaesthesia was associated with similar decreases in $\dot{V}O_2$ in the two groups (−19% in the

Table 1 Patient characteristics and operative data (mean (SD or range) or number). No significant difference between the two groups

	Saline group ($n = 9$)	Enalapril group ($n = 11$)
Patient characteristics		
Age (yr)	68 (53–79)	69 (55–81)
Sex (M/F)	7/2	10/1
Body surface area (m²)	1.74 (0.21)	1.82 (0.11)
Aortic aneurysm (n)	2	2
Hypertensive disease (n)	8	10
Coronary artery disease (n)	3	4
History of pulmonary oedema (n)	1	0
Creatinine clearance (ml min^{-1} 1.73 m^{-2})	87 (21)	77 (19)
Preoperative drug therapy		
β blockers (n)	5	5
Ca^{2+}-channel blockers (n)	3	5
Diuretics (n)	1	2
Intraoperative data		
Cross-clamping time (min)	69 (26)	74 (23)
Duration of surgery (min)	300 (78)	292 (46)
Packed red cells (ml)	311 (314)	487 (413)
Crystalloids (litre h^{-1})	1.76 (0.21)	1.97 (0.45)

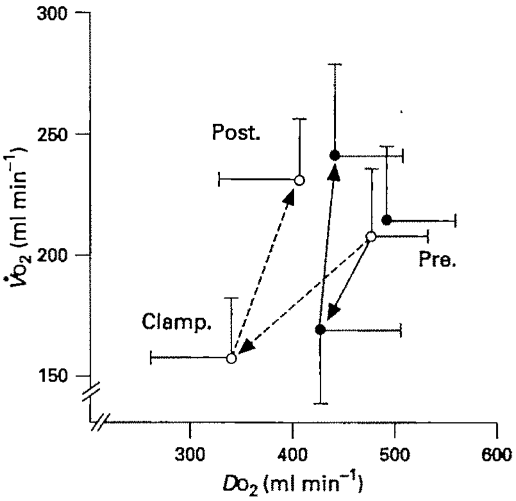


Figure 1 Changes in systemic oxygen delivery (DO_2) and oxygen consumption ($\dot{V}O_2$) in the saline (○) and enalapril (●) groups. Data represent mean (SD) values of averaged DO_2 and $\dot{V}O_2$ measured before (Pre.) (2 min after incision and 2 min before aortic cross-clamping), during (clamp.) (5 min after aortic clamping and before aortic unclamping) and after (Post.) 2 min after unclamping and at peritoneal closure) aortic cross-clamping.

Table 2 Mean (SD) systemic haemodynamic and metabolic data in the saline ($n = 9$) and enalapril ($n = 11$) groups. *$P < 0.05$ compared with saline group; †$P < 0.05$, ‡‡$P < 0.01$ compared with pre-anaesthesia baseline; §$P < 0.05$ compared with "2 min before aortic clamping" period

		Pre-anaesthesia		Pre-clamping		Aortic cross-clamping		Post-clamping	
Variable	Group	Baseline	20 min after drug	2 min after incision	2 min before aortic clamping	5 min after aortic clamping	Before vascular unclamping	2 min after unclamping	At peritoneal closure
Heart rate	Saline	76 (7)	74 (7)	80 (12)	80 (10)	84 (13)	83 (11)	86 (12)	81 (11)
(beat min^{-1})	Enalapril	71 (12)	72 (13)	81 (17)	69 (9)	71 (13)	72 (14)	72 (15)	77 (14)
Mean arterial	Saline	101 (9)	100 (7)	89 (11)	93 (10)	95 (17)	89 (12)	79 (10)†	82 (8)†
pressure (mm Hg)	Enalapril	94 (10)	93 (11)	90 (16)	86 (7)	87 (13)	79 (9)†	75 (12)†	81 (11)†
Cardiac index	Saline	3.3 (0.3)	3.5 (0.3)	3.2 (0.2)	3.2 (0.3)	2.6 (0.3)††§	2.7 (0.3)†§	3.2 (0.6)	3.2 (0.5)
(litre min^{-1} m^{-2})	Enalapril	3.0 (0.4)	3.4 (0.6)††	3.2 (0.8)	3.3 (0.8)	3.2 (0.8)	3.4 (0.7)*	3.5 (1.0)	3.5 (0.9)
Systemic vascular	Saline	2253 (327)	2111 (342)	1941 (293)	2052 (386)	2646 (733)§	2383 (601)	1837 (538)	1792 (335)†
resistance index (dyn s cm^{-5} m^{-2})	Enalapril	2349 (451)	2080 (430)	2154 (736)	1913 (525)†	1948 (451)†	1651 (420)*††	1570 (606)††	1682 (487)†
Systemic O_2	Saline	486 (93)	499 (62)	422 (72)	482 (65)	335 (64)††§	348 (67)††§	412 (72)	419 (83)
delivery (ml min^{-1})	Enalapril	478 (93)	519 (101)	446 (102)	496 (102)	447 (111)*	433 (121)	445 (124)	452 (127)
Systemic O_2	Saline	251 (33)	248 (27)	206 (42)††	214 (30)††	168 (38)††§	169 (35)††§	232 (28)	243 (30)
consumption (ml min^{-1})	Enalapril	267 (47)	260 (45)	215 (32)††	217 (42)††	172 (31)††§	179 (30)††§	241 (46)	246 (44)
Mixed venous O_2	Saline	73 (4)	74 (4)	72 (6)	74 (5)	65 (6)§	67 (5)	66 (6)	66 (4)
saturation (%)	Enalapril	71 (7)	76 (5)†	76 (5)	76 (4)†	75 (5)	74 (4)†	69 (6)	70 (3)

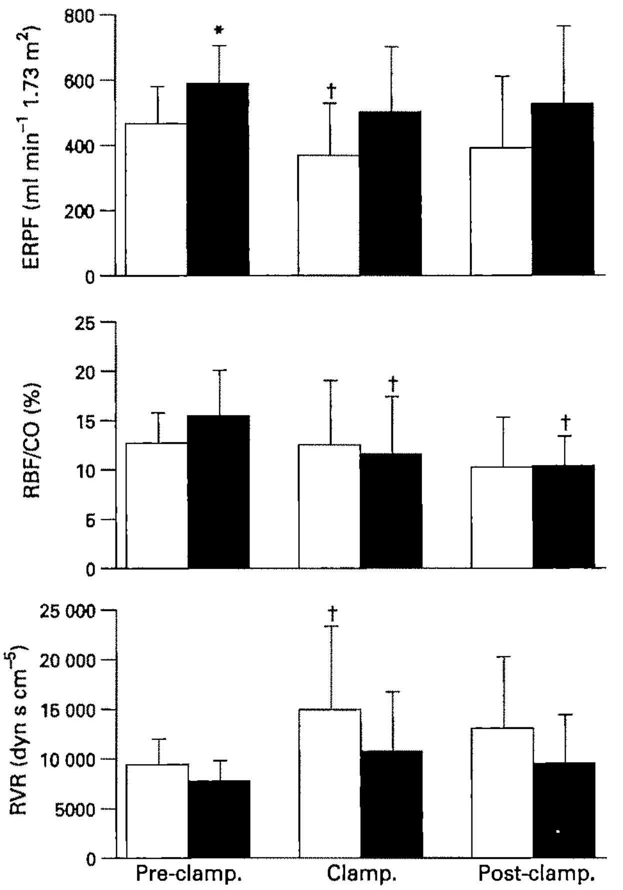


Figure 2 Effective renal plasma flow (ERPF), fractional renal blood flow (% RBF/CO) and renal vascular resistance (RVR) at the pre-clamping, clamping and post-clamping periods, in the saline (☐) and enalapril (■) groups. $*P < 0.05$ compared with saline group; $\dagger P < 0.05$ compared with pre-clamping.

saline group and −16% in the enalapril group). Two patients in the enalapril group and one in the saline group required an i.v. bolus of phenylephrine 100 μg after induction of anaesthesia.

There was no significant difference in HR or MAP between the two groups at any time. Towards the end of surgery, MAP and SVRI were decreased significantly in the two groups, compared with pre-anaesthesia baseline values.

In the saline group, aortic cross-clamping induced a decrease in CI (−29%; $P = 0.001$); the associated reduction in $\dot{D}o_2$ (−28%) correlated with the reduction in $\dot{V}o_2$ (−24%; $P < 0.001$; $r = 0.85$) and was accompanied by decreased oxygen saturation in mixed venous blood ($S\bar{v}_{O_2}$, −9%; $P = 0.030$). In contrast, in the enalapril group, CI was maintained at pre-clamping values and the reduction in $\dot{V}o_2$ (−20%; $P < 0.001$) induced by aortic cross clamping was not associated with significant changes in $\dot{D}o_2$ or $S\bar{v}_{O_2}$. After aortic unclamping, $\dot{V}o_2$ increased to pre-clamping values in the two groups; this was accompanied by a significant increase in $\dot{D}o_2$ in the saline group only (+19%; $P = 0.034$).

RENAL HAEMODYNAMIC VARIABLES AND FUNCTION (fig. 2, table 3)

During the pre-clamping period, in enalapril-treated patients, C_{Creat} was increased compared with the preoperative period (+27%; $P = 0.035$) and higher ERPF values were noted compared with saline-treated patients ($P = 0.027$).

In the saline group, aortic cross-clamping was associated with significant decreases in C_{Creat}, C_{IN} and ERPF, whereas the fraction of CO (RBF/CO ratio) delivered to the kidney did not change. In the enalapril group, after aortic cross-clamping, the RBF/CO ratio decreased significantly and GFR was greater than in the saline group, as indicated by C_{Creat} (78 (28) *vs* 53 (17) ml min^{-1} 1.73 m^{-2}; $P = 0.052$) and C_{IN} (79 (32) *vs* 49 (22) ml min^{-1} 1.73 m^{-2}; $P = 0.033$). The simultaneous changes in systemic and renal haemodynamic variables resulted in unchanged RVR in the enalapril group whereas renal vasoconstriction occurred in the saline group, as indicated by increases in RVR ($P = 0.044$). In both groups, a positive linear relationship was found between aortic clamping-induced changes in ERPF and GFR ($r = 0.83$ in the saline group and $r = 0.65$ in the enalapril group). No such relationship was found between CI and ERPF and between CI and GFR.

After vascular unclamping and until 24 h after surgery, C_{Creat} values in the saline group remained

Table 3 Mean (SD) renal functional data in the saline ($n = 9$) and enalapril ($n = 11$) groups. $*P < 0.05$ compared with saline group; $\dagger P < 0.05$, $\dagger\dagger P < 0.01$ compared with preoperative period; $\S P < 0.05$ compared with pre-clamping period

			Surgery			
Variable	Group	Preoperative	Pre-clamping	Aortic clamping	Post-clamping	Postoperative
Creatinine clearance (ml min^{-1} 1.73 m^{-2})	Saline	87 (21)	76 (34)	53 (17)†§	59 (26)†§	64 (22)†
	Enalapril	77 (19)	97 (28)†	78 (28)§	80 (33)	88 (23)†
Urinary flow (ml min^{-1})	Saline	0.7 (0.3)	1.8 (1.0)	1.2 (0.6)	2.1 (2.4)†	1.5 (0.3)†
	Enalapril	0.8 (0.3)	3.0 (1.8)†	3.6 (2.1)†	3.7 (2.3)†	1.6 (0.6)††
Free water clearance (ml min^{-1})	Saline	−0.8 (0.2)	−0.2 (0.8)	−0.3 (0.3)†	−0.6 (0.8)	−0.6 (0.2)
	Enalapril	−0.9 (0.2)	−1.1 (1.0)	−1.0 (0.7)	−0.8 (1.0)	−1.0 (0.9)
Proteinuria (mg min^{-1})	Saline	0.08 (0.05)	0.61 (0.50)†	1.19 (1.06)†	2.42 (2.54)†	1.08 (0.98)†
	Enalapril	0.12 (0.05)	1.10 (1.03)†	1.29 (1.98)†	3.12 (4.21)†	1.44 (1.32)†
Na^+ fractional excretion (%)	Saline	0.3 (0.2)	2.4 (1.2)††	2.4 (1.1)††	3.4 (2.1)††	2.4 (1.6)††
	Enalapril	0.4 (0.2)	3.1 (2.1)††	3.7 (3.4)††	4.3 (3.3)††	1.7 (1.2)††
Na^+ urinary excretion (μEq/min)	Saline	39 (30)	207 (121)†	145 (90)†	245 (125)†	163 (63)†
	Enalapril	44 (33)	400 (135)††	453 (201)††	502 (375)††	173 (90)†

significantly lower than during the preoperative period. In contrast, in the enalapril group, C_{Creat} did not differ from preoperative values, and postoperative C_{Creat} was significantly higher than in the saline group. During operation, urinary output was comparable, whereas FE_{Na^+}, U_{Na^+} and proteinuria were significantly increased compared with preoperative values in the two groups.

We found a close correlation between C_{IN} and C_{Creat} ($r = 0.89$; $n = 59$; $P < 0.001$) and no significant change in E_{PAH} at the three intraoperative study times.

All patients survived the operation; the trachea was extubated in the operating theatre and they were monitored in a post-anaesthesia recovery unit for 24 h. No patient had ECG evidence of myocardial infarction and no episode of delayed renal failure occurred until discharge from hospital in the two groups.

Discussion

In this study we have demonstrated that preoperative administration of enalapril, a long-acting ACEI, prevented the decrease in CI and Do_2 induced by infrarenal aortic cross-clamping, without influencing changes in oxygen uptake. Acute RAS block is associated with improved intraoperative renal perfusion and better preservation of GFR, lasting at least 24 h after surgery.

We administered enalapril in an unusually high dose (50 µg kg^{-1}) with the aim of inhibiting plasma ACE activity, and hence angiotensin II synthesis, for at least 24 h. Indeed, elevated PRA has been reported after surgical incision and increased angiotensin II plasma concentrations are known to culminate at the time of unclamping and to persist for more than 6 h after operation [9, 10, 14]. We also found that lower enalapril doses (10 and 30 µg kg^{-1}) did not afford suppression of plasma ACE activity for the whole perioperative period.

Acute removal of angiotensin II vasopressor effects could potentially contribute to intraoperative hypotension because of synergistic effects between ACEI and other chronic antihypertensive drugs given before operation. Surprisingly, acute block of the RAS was associated with a stable haemodynamic state and there were no differences in vasopressor and fluid requirements between the two groups. We believe that haemodynamic tolerance to enalapril pretreatment was attributed to optimal i.v. fluid loading. In addition, the other arterial pressure regulating mechanisms (the sympathetic nervous system and arginine vasopressin), were either unaffected or blocked incompletely; hence, these mechanisms were presumably activated after surgical incision, to maintain arterial pressure homeostasis after withdrawal of the vasoconstricting influence of angiotensin II [15].

In accordance with previous investigations [16], we observed a marked decrease in CO (−29%) despite stable arterial and cardiac filling pressures after exclusion of the lower body compartment in saline-treated patients. Several physiological mechanisms are thought to be implicated in the haemodynamic changes associated with aortic cross-clamping. First, mechanical occlusion of the aorta directly increases cardiac afterload whereas activation of the sympathetic nervous system and the RAS results in increased arteriolar vasomotor tone and myocardial contractility. Second, using radioisotopic techniques, it has been shown that blood volume is redistributed from the lower body to the more compliant splanchnic compartment [17]. Third, decreased right ventricular end-diastolic volume has been reported, despite unchanged cardiac filling pressures, suggesting lower cardiac preload associated with reduced ventricular diastolic compliance [18]. Taken together these data suggest that the reduction in CO results mainly from reduced blood flow return to the heart (partly attributed to the slower time constant of blood flow within the splanchnic compartment) combined with a sudden increase in impedance to blood flow as a result of mechanical aortic occlusion and arteriolar vasoconstriction. Interestingly, several studies have demonstrated less haemodynamic changes after aortic cross-clamping in patients with aorto-occlusive disease than in those with abdominal aortic aneurysm. It is currently believed that the amount of collateral vascularization in patients with aorta-occlusive disease could afford some protection against major reductions in CO and increases in arterial pressure after aortic cross-clamping [19].

An important finding of this study was that enalapril pretreatment prevented the decrease in cardiac output induced by aortic cross-clamping. Experimental data suggest that the splanchnic vascular bed is extremely sensitive to vasoconstrictor agents, including catecholamines and angiotensin II, particularly during pathological conditions such as hypovolaemia or cardiac failure [20–22]. Acute administration of ACEI in dogs with congestive heart failure has also been shown to increase the unstressed splanchnic vascular volume and to improve circulatory output by promoting active vasodilatation [23]. Based on these results, we speculate that block of the RAS prevented the reduction in CI by alleviating elevated angiotensin II-dependent vascular impedance and hence by promoting "adaptive" splanchnic vasodilatation to accommodate for the sudden shift in blood volume from the lower to the upper body compartment. Other vasodilatators such as nifedipine [24], urapidil [25] and nitroglycerine [26] were also found to reverse the decrease in cardiac output induced by cross-clamping; however, in contrast with ACEI, they are associated with increased sympathetic discharge, that may affect the extent and pattern of changes in blood volume redistribution and in haemodynamic response.

Although pretreatment with enalapril produced maintenance of CI and Do_2, $\dot{V}o_2$ decreased similarly during infrarenal clamping in the two groups. Gelman and co-workers [25] reported similar results when nitroglycerine was infused at a rate of 1 to 2 µg kg^{-1} min^{-1} in order to maintain cardiac output. As whole body oxygen utilization was not restored after the pharmacologically induced increase in Do_2, we assume that maximal vasorelaxation had already occurred in ischaemic tissues located below the aortic clamp (in response to local vasodilators) and that enalapril (and nitroglycerine) increased shunt blood flow in the upper body compartment with no improvement in nutritive flow or tissue oxygen extraction, or both. Hence, systemic oxygen supply was matched adequately to the cross-clamp "adapted $\dot{V}O_2$" in the saline group whereas "unnecessary" elevated oxygen supply and myocardial work were achieved during aortic cross-clamping in the enalapril group.

Considering the stimulatory effects of surgical stress on the RAS and the potent renal vasoconstrictor effects of angiotensin II, it was not surprising to find that suppression of circulating and, presumably, intrarenal angiotensin II generation in enalapril-treated patients was associated with higher ERPF (a mean difference of 17%) compared with saline-treated patients. Animal studies have demonstrated that enhanced renal blood flow was the most impressive regional haemodynamic change after administration of different types of ACEI [26]; blood flow within the inner cortex was predominantly increased and accompanied by enhanced GFR [27]. The renal haemodynamic actions of ACEI have at least two components: suppression of angiotensin II synthesis and prolongation of bradykinin half-life through inhibition of its degradation. This latter component is thought to mediate renal vasodilatation even when RAS activation is prevented by preoperative β blocker treatment [28], as renin secretion from the juxtaglomerular cells is dependent on β_1 receptor stimulation.

Before aortic cross-clamping, ACEI-treated patients had higher GFR compared with saline-treated patients, because of higher ERPF as increased cortical blood flow would transform "silent" nephrons into new filtering units. During aortic cross-clamping, a reduction in GFR occurred in both groups and the changes in GFR correlated positively with changes in ERPF, indicating that the neurohumoral mediators that regulate renal haemodynamic state ultimately influence glomerular filtration properties. Deterioration of systemic haemodynamic state and release of vasoconstrictor mediators such as angiotensin II, thromboxane A_2 and endothelin-1 after aortic cross-clamping are believed to contribute to impaired renal function [29]. In this study, maintenance of GFR in enalapril-treated patients could be attributed to a lesser decrease in ERPF or to an increase in the glomerular ultrafiltration coefficient as a consequence of the withdrawal of the constricting effects of angiotensin II on mesangial cells, or both. Endothelin-1 has several additional synergistic interactions with the RAS, including enhanced ACE activity (conversion of angiotensin I to angiotensin II), potentiation of endothelin constriction by angiotensin II and activation of endothelin-1 synthesis by angiotensin II. The clinical importance of these interactions has recently been emphasized by demonstration that ACEI pretreatment abolishes renal vasoconstriction and the decrease in GFR induced by endothelin-1 [30].

In the saline group, GFR remained depressed after aortic unclamping, at a time when CI had recovered to pre-clamping values. Adenosine and oxygen-derived free radicals liberated from the ischaemic reperfused tissues are potential candidates for this transient renal dysfunction. Adenosine requires a normally functioning RAS to mediate its pre-glomerular vasoconstrictor action and administration of an ACEI has been shown to attenuate adenosine-mediated vasoconstriction [31]. Colson and co-workers [32] studied patients who received enalapril 10 mg orally, for 2 days before undergoing vascular surgery during i.v. anaesthesia. In agreement with our results, they found lesser haemodynamic changes induced by aortic cross-clamping in the treated group. However, there was no positive effect on renal haemodynamic state or function, as assessed from clearance of ^{99}technetium-diethylenetriaminepenta-acetic acid and ^{131}iodo-hippuran, respectively. Differences in dose regimen, anaesthetic management and measurements methods could account for these contradictory results.

In summary, we have demonstrated that a single i.v. dose of enalapril can be administered safely in patients undergoing elective abdominal aortic surgery when optimal fluid loading is maintained. This pretreatment is associated with suppression of the aortic clamping-induced reduction in cardiac output, renal vasodilatation and better preservation of glomerular filtration. Oxygen consumption decreased markedly after aortic-clamping, despite ACEI-induced maintenance of systemic oxygen supply. The renoprotective effect of enalapril could be attributed to withdrawal of the constricting action of angiotensin II, reduced kinin degradation and antagonism of endothelin-1. These effects would also be potentially helpful in patients undergoing suprarenal aortic cross-clamping or kidney transplantation. However, it should be kept in mind that ACE inhibitors could precipitate onset of renal failure in hypovolaemic subjects or in the presence of renal artery stenosis. Before suggesting specific indications, further studies are needed to define in which population subgroups RAS block may be beneficial.

References

1. Gelman S. The pathophysiology of aortic cross-clamping and unclamping. *Anesthesiology* 1995; **82**: 1026–1060.
2. Gamulin Z, Forster A, Morel DR, Simonet F, Aymon E, Favre H. Effects of aortic cross-clamping on renal hemodynamics in humans. *Anesthesiology* 1984; **61**: 394–399.
3. Paul MD, Mazer CD, Byrick RJ, Rose DK, Goldstein MB. Influence of mannitol and dopamine on renal function during elective infrarenal aortic clamping in man. *American Journal of Nephrology* 1986; **6**: 427–434.
4. Gamulin Z, Forster A, Simonet F, Aymon E, Favre H. Effects of renal sympathetic blockade on renal hemodynamics in patients undergoing major aortic abdominal surgery. *Anesthesiology* 1986; **65**: 688–692.
5. Huval WV, Lelcuk S, Allen PD, Mannick JA, Shepro D, Hechtman HB. Determinants of cardiovascular stability during abdominal aortic aneurysmectomy (AAA). *Annals of Surgery* 1984; **199**: 216–222.
6. Casthely PA, Diunezki, J, Jones R, Goodman K, Redko V, Cottrell JE, Yoganathan T, Fiordalisi J. Superoxide dismutase and hemodynamic changes following aortic cross clamp release. *Journal of Cardiothoracic Anesthesia* 988; **2**: 450–454.
7. Antonucci F, Bertolissi M, Calo L. Plasma endothelin and renal function during infrarenal aortic cross-clamping and nifedipine infusion. *Lancet* 1990; **336**: 1449.

8. Mirenda JV, Grissom TE. Anesthetic implications of the renin–angiotensin system and angiotensin-converting enzyme inhibitors. *Anesthesia and Analgesia* 1991; 72: 667–683.
9. Dzau VJ. Tissue renin–angiotensin system: Physiologic and pharmacologic implications. *Circulation* 1988; 77(Suppl. 1): 1–3.
10. Gal TJ, Cooperman LH, Berkowitz HD. Plasma renin activity in patients undergoing surgery of the abdominal aorta. *Annals of Surgery* 1974; **178**: 65–69.
11. Grindlinger GA, Vegas AM, Manny J, Bush HL, Mannick JA, Hechtman HB. Volume loading and vasodilators in abdominal aortic aneurysmectomy. *American Journal of Surgery* 1980; **139**: 480–486.
12. Kostis JB. Angiotensin-converting enzyme inhibitors. II. Clinical use. *American Heart Journal* 1988; **116**: 1591–1605.
13. Hollenberg NK, Raij L. Angiotensin-converting enzyme inhibition and renal protection. An assessment of implications for therapy. *Archives of Internal Medicine* 1993; **153**: 2426–2435.
14. Grindlinger GA, Vegas AM, Williams GH, Mannick JA, Hechtman HB. Independence of renin production and hypertension in abdominal aortic aneurysmectomy. *American Journal of Surgery* 1981; **141**: 475–477.
15. Udelsman R, Norton JA, Jelenich SE, Goldstein DS, Linehan WM, Loriaux DL, Chrousos GP. Response of the hypothalamic–pituitary adrenal and renin–angiotensin axes and the sympathetic system during controlled surgical and anesthetic stress. *Journal of Clinical Endocrinology and Metabolism* 1987; **64**: 986–994.
16. Falk JL, Rackow EC, Blumenberg R, Gelfand M, Fein IA. Hemodynamic and metabolic effects of abdominal aortic crossclamping. *American Journal of Surgery* 1981; **142**: 174–177.
17. Gelman S, Khazaeli MB, Orr R, Henderson T. Blood volume redistribution during crossclamping of the descending aorta. *Anesthesia and Analgesia* 1994; **78**: 219–224.
18. Vandermeer TJ, Maini BS, Hendershott TH, Sottile FD. Evaluation of right ventricular function during aortic surgery. *Archives of Surgery* 1993; **128**: 582–585.
19. Johnston WE, Balestrieri FJ, Plonk G, D'Souza V, Howard G. The influence of periaortic collateral vessels on the intraoperative hemodynamic effects of acute aortic occlusion in patients with aorto-occlusive disease or abdominal aortic aneurysm. *Anesthesiology* 1987; **66**: 386–389.
20. Reilly PM, Bulkley GB. Vasoactive mediators and splanchnic perfusion. *Critical Care Medicine* 1993; **21**(Suppl. 1): S55–S68.
21. Stockland O, Thorvaldsen A, Ilebekk A, Kiil F. Mechanisms of blood pressure elevation during angiotensin infusion. *Acta Physiologica Scandinavica* 1982; **15**: 455–465.
22. Risoe C, Hall C, Smiseth OA. Effect of enalaprilat on splanchnic vascular capacitance during acute ischemic heart failure in dogs. *American Journal of Physiology* 1994; **266**: H2182–H2189.
23. Derrer SA, Bastulli JA, Baele H, Rhodes RS, Dauchot PJ. Effects of nifedipine on the hemodynamic response to clamping and declamping of the abdominal aorta in dogs. *Journal of Cardiothoracic Anesthesia* 1989; **3**: 58–64.
24. Van Hemelrijk J, Waets P, Van Aken H, Lacroix H, Nevelsteen A, Suy R. Blood pressure management during aortic surgery: urapidil compared to isosorbide dinitrate. *Journal of Cardiothoracic Anesthesia* 1993; **7**: 273–278.
25. Gelman S, McDowell H, Varner PD, Pearson J, Ebert J, Graybar G, Proctor J. The reasons for cardiac output reduction after aortic cross-clamping. *American Journal of Surgery* 1988; **155**: 578–586.
26. Richer C, Dousseau M-P, Giuducelli JF. Systemic and regional hemodynamic profile of five angiotensin I converting enzyme inhibitors in the spontaneously hypertensive rat. *American Journal of Cardiology* 1987; **59**: 12D–17D.
27. Noguchi K, Ojiri Y, Chibana T, Sakanashi M. Simultaneous measurement of renal blood flow of the outer and inner cortex by laser-Doppler flowmetry in anesthetized dogs: Effects of enalapril diacid. *Archives Internationales de Pharmacodynamie et de Therapie* 1992; **320**: 68–80.
28. Grant RP, Jenkins LC. Modification by preoperative beta-blockade of the renin response to infrarenal aortic cross-clamping. *Canadian Anaesthesia Society Journal* 1983; **30**: 480–486.
29. Apperloo AJ, de Zeeuw D, de Jong PE. Discordant effects of enalapril and lisinopril on systemic and renal hemodynamics. *Clinical Pharmacology and Therapeutics* 1994; **56**: 647–658.
30. Chan DP, Clavell A, Keiser J, Burnett JC. Effects of renin–angiotensin system in mediating endothelin-induced renal vasoconstriction; therapeutic implications. *Journal of Hypertension* 1994; **12**: S43–S49.
31. Hall JE, Granger JP, Hester RL. Interaction between adenosine and angiotensin II in controlling glomerular filtration. *American Journal of Physiology* 1985; **248**: F340–F346.
32. Colson P, Ribstein J, Seguin JR, Marty-Ane C, Roquefeuil B. Mechanisms of renal hemodynamic impairment during infrarenal aortic cross-clamping. *Anesthesia and Analgesia* 1992; **75**: 18–23.

British Journal of Anaesthesia 1996; 76: 640–644

Laparoscopic cholecystectomy: haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position†

E. O'LEARY, K. HUBBARD, W. TORMEY AND A. J. CUNNINGHAM

Summary

We have assessed the potential for myocardial ischaemia during laparoscopic cholecystectomy in 16 otherwise healthy patients. Continuous ambulatory ECG monitoring was commenced 12 h before operation and continued for 24 h after operation. The neuroendocrine stress response was assessed by measuring plasma concentrations of adrenaline and noradrenaline, human growth hormone, cortisol, renin and aldosterone, and prolactin, at specified times during surgery. Acute ST segment changes in the ECG occurred in only two patients. These episodes were independent of creation of pneumoperitoneum and changes in position. Acute intraoperative increases in MAP were noted during insufflation of carbon dioxide and reverse Trendelenburg positioning ($P < 0.05$). A four-fold increase in plasma concentrations of renin and aldosterone was noted after pneumoperitoneum and reverse Trendelenburg positioning ($P > 0.05$). There was a linear correlation between changes in plasma renin and aldosterone concentrations and MAP ($r = 0.97$ and $r = 0.85$, respectively). Prolactin concentrations increased four-fold after induction of anaesthesia. Cortisol, HGH, adrenaline and noradrenaline concentrations increased after deflation of the pneumoperitoneum. The time profile–concentration changes of increased MAP and renin–aldosterone suggests a cause–effect relationship. Increased intra-abdominal pressure and reverse Trendelenburg positioning may reduce cardiac output and renal blood flow. The early increase in prolactin concentration was probably secondary to the effect of the opioid fentanyl. (*Br. J. Anaesth.* 1996; **76**: 640–644)

Key words

Monitoring, electrocardiography. Cardiovascular system, effects. Hormones, renin. Hormones, aldosterone. Surgery, hormonal response. Surgery, laparoscopy. Position, effects. Position, Trendelenburg.

Laparoscopic cholecystectomy has four potential causes of major physiological changes in the anaesthetized patient: initial Trendelenburg position, creation of the pneumoperitoneum, potential for systemic absorption of carbon dioxide and reverse Trendelenburg position [1].

The extent of the cardiovascular changes associated with the creation of pneumoperitoneum depends on the intra-abdominal pressure attained, volume of carbon dioxide absorbed, patient's intravascular volume, ventilatory technique, surgical conditions and anaesthetic agents used [2, 3]. The haemodynamic effects include an increase in mean arterial pressure (MAP), decrease in cardiac output (CO) and increase in systemic vascular resistance (SVR).

Induction of pneumoperitoneum and changes in position appear to be associated with a biphasic haemodynamic response, with an early reduction followed by partial recovery of cardiac index [4]. Joris and colleagues [5] used flow-directed pulmonary artery catheters to assess the haemodynamic effects of peritoneal carbon dioxide insufflation to an intra-abdominal pressure (IAP) of 14 mm Hg in healthy non-obese patients with no cardiac disease. Cardiac index was reduced to 50% of its preoperative value 5 min after the beginning of insufflation. The relative roles of the factors which contribute to changes in CO are difficult to separate, but may include mechanical factors and neurohumoral responses [5, 6]. Increased venous resistance and compression of the abdominal aorta may contribute to the increase in cardiac afterload. Potential mediators of increased SVR include catecholamines, prostaglandins, the renin–angiotensin system and vasopressin [5, 7, 8]. During pneumoperitoneum, plasma concentrations of dopamine, vasopressin, adrenaline, noradrenaline, renin and cortisol increase significantly. Of particular interest is the time course of the increase in vasopressin and noradrenaline. The plasma time course profile parallels that of changes in CI, MAP and SVR, suggesting a possible cause and effect relationship.

In this study, we quantified some of the neuroendocrine stress responses during and after pneumoperitoneum and also the incidence of intraoperative ST segment changes in the ECG.

Patients and methods

After obtaining local Ethics Committee approval, we studied 16 consecutive patients, free of cardiac

---

ELEANOR O'LEARY*, FFARCSI, ANTHONY J. CUNNINGHAM, MD, FRCPC, FFARCSI, Royal College of Surgeons in Ireland, Dublin, Ireland. KAREN HUBBARD, SRN, WILLIAM TORMEY, FRCPI, Beaumont Hospital, Dublin, Ireland. Accepted for publication: January 8, 1996.

*Address for correspondence: Department of Anaesthesia, St George's Hospital Medical School, Jenner Wing, Tooting, London SW17 0RE.

†Presented in part at the European Society of Anaesthesiology, Paris, April 1995.

disease, undergoing elective laparoscopic cholecystectomy. Preoperative assessment included history and physical examination, specifically documenting the presence of ischaemic heart disease, for example previous myocardial infarction (MI), angina, left ventricular failure (LVF) or hypertension. Preoperative investigations included full blood count, urea and electrolyte concentrations, chest x-ray and resting 12-lead electrocardiograph (ECG).

Exclusion criteria included patients with documented ischaemic heart disease (history of angina, previous MI, hypertension) or signs of left ventricular failure. Patients who refused to participate and those in whom ECG interpretation was difficult, that is pre-existing left bundle branch or left ventricular hypertrophy with strain, and patients with hypokalaemia or those receiving digoxin therapy were also excluded from the study.

Continuous ambulatory electrocardiographic (CAECG) monitoring was commenced the evening before surgery and continued for 30 h after operation. Ambulatory ECG monitoring was performed using a Reynolds Medical Tracker model using leads II and V_5. A Reynolds Medical Pathfinder, Mark111, 24-h Holter monitoring system, incorporating Reynolds Medical version 2.2 software and hardware system, was used for analysis of ST segment changes. The Holter tape was run through the system for the full 24 h (or the duration of the tape). The software produces a trend or graph of ST changes against time for the duration of the recording. A reference ST level is determined and all ST changes are calibrated to this (the reference ST is usually calibrated using patients' resting ST level). Changes are not considered significant unless greater than ± 1 mm from the reference. All ST changes were printed with an accompanying ECG strip. The software system is heavily dependent on human intervention. For the purpose of standardizing intraoperative management and indications for treatment, tachycardia was considered as 20 % above the mean preoperative heart rate or 90 beat min^{-1}. Acute changes in heart rate and arterial pressure had to be $\geqslant 4$ min duration. Myocardial ischaemia was defined as > 0.1 mV or more positive or negative horizontal ST segment shift, which extended at least 80 ms beyond the J point of the QRS and was at least 1 min duration. Heart rate, arterial pressure and ST segment analysis were measured for a minimum of 12 h before operation, during operation and for 24 h after operation.

A standard general anaesthetic technique was used for all patients. Patients were premedicated with diazepam 10 mg orally, 1 h before surgery. Anaesthesia was induced with fentanyl 1–2 $\mu\text{g kg}^{-1}$ and thiopentone 3–4 mg kg^{-1}. Vecuronium 0.1 mg kg^{-1} was administered to facilitate tracheal intubation. Anaesthesia was maintained with 0.5–1 % end-tidal isoflurane and 50 % nitrous oxide in oxygen. Intraoperative monitoring included continuous ECG, systemic arterial pressure using an automated cuff, pulse oximetry, inspired oxygen fraction and peak airway pressure. Intermittent positive pressure ventilation was used with an Ohmeda volume cycle ventilator maintaining the end-tidal carbon dioxide partial pressure at 4–5.3 kPa. Intraoperative i.v. fluids were administered at 3 $\text{ml kg}^{-1}\ \text{h}^{-1}$.

The surgical technique involved intraperitoneal insufflation of carbon dioxide via a Verres needle inserted into a small umbilical incision in the 15–20° Trendelenburg position. An electronic variable-flow insufflator terminated flow when the intra-abdominal pressure reached 15 mm Hg. A cannula was inserted in place of the needle to provide and maintain insufflation adequate for surgery. A video laparoscope was inserted through the cannula and the operative field was seen. The patient's position was changed to steep reverse Trendelenburg, with lateral tilt, to facilitate retraction of the gall bladder fundus.

Neuroendocrine stress responses were assessed by measuring resting plasma concentrations of adrenaline and noradrenaline, renin and aldosterone, prolactin, growth hormone and cortisol in 20-ml blood samples obtained via a catheter inserted in the antecubital fossa. Samples were obtained on the evening before surgery (T1), before induction (T2), after induction (T3), 5 min before insufflation of carbon dioxide (T4), 5 min after insufflation of carbon dioxide (T5), 5 min after tilting in the reverse Trendelenburg position (T6) and after exsufflation in the recovery room (T7). Plasma adrenaline and noradrenaline concentrations were measured by high pressure liquid chromatography with electrochemical detection [5]. The sensitivity of both assays was 10 pg ml^{-1} and intra-assay and inter-assay coefficients of variation were 5 % and 8 %, respectively, for both. Human growth hormone, cortisol and aldosterone concentrations were measured by direct radioimmunoassay with a sensitivity of 0.5 ng litre^{-1}, 30 nmol litre^{-1} and 6.0 pg ml^{-1}, respectively. The intra-assay and inter-assay coefficients of variation were 6.3 % and 13.1 %, 11.2 % and 13.5 %, and 4.12 % and 3.82 %, respectively. Plasma renin activity was measured as the amount of angiotensin produced in $\text{ng ml}^{-1}\ \text{h}^{-1}$. The sensitivity of this assay was 0.039 ng ml^{-1} and the intra-assay and inter-assay coefficients were 5.82 % and 4.82 %, respectively. Prolactin was measured by immunofluorometric assay with a sensitivity of 9 miu litre^{-1} and the intra-assay and inter-assay coefficients of variation were 4.3 % and 6.5 %, respectively.

Perioperative cardiac morbidity was defined as including the presence of myocardial ischaemia, unstable angina, arrhythmias, congestive heart failure or death. History, physical examination, daily 12-lead ECG and cardiac specific enzymes were performed before operation and after surgery for 2 days. Criteria for diagnosing an MI included serial ECG and cardiac enzymes. Criteria for diagnosing left ventricular failure included chest pain, a gallop rhythm or basal crepitations. Daily ECG were performed noting the presence of new Q waves > 0.04 s and > 1 mm deep, or new left bundle branch block (LBBB). Measurement of serial cardiac enzymes was performed and a creatine kinase MB fraction (CK-MB) greater than 8 %, using an immunoinhibition method, was considered indicative of myocardial damage.

Data are expressed as mean (SD). Data were analysed by one-way analysis of variance for repeated measures (ANOVA) followed by Scheffé's *post hoc* tests. For inter-group comparisons, $P < 0.05$ was considered significant.

Results

We studied 16 (12 females) ASA I–II patients, mean age 40 (range 24–72) yr. Mean duration of surgery was 94 (SD 30) min (table 1).

Ambulatory ECG recordings revealed that patient No. 4 had an episode of acute ST segment changes before insufflation of carbon dioxide. This was associated with hypotension (MAP 45 mm Hg) and bradycardia (heart rate of 38 beat min^{-1}), which responded to i.v. fluids and atropine. Patient No. 8 had an episode of ST segment changes which began during exsufflation of carbon dioxide and continued for 69 min. Serial ECG, cardiac enzymes and physical examination for 2 days after operation revealed no evidence of cardiac morbidity in either patient. No abnormalities were detected in the recordings of the other 14 patients.

There were no significant changes in heart rate throughout the study. There was a significant increase in MAP after insufflation of carbon dioxide and reverse Trendelenburg positioning ($P = 0.01$ and 0.0003 respectively) (fig. 1).

Plasma concentrations of noradrenaline increased after exsufflation of carbon dioxide. However, this increase was not statistically significant ($P = 0.48$). Plasma concentrations of adrenaline increased after reverse Trendelenburg and exsufflation of carbon dioxide. Again, these increases were not statistically significant (fig. 2).

Table 1 Patient data (mean (SD or range) or number)

n	16
Age (yr)	40 (24–72)
Sex (M/F)	4/12
Duration of surgery (min)	94 (30)

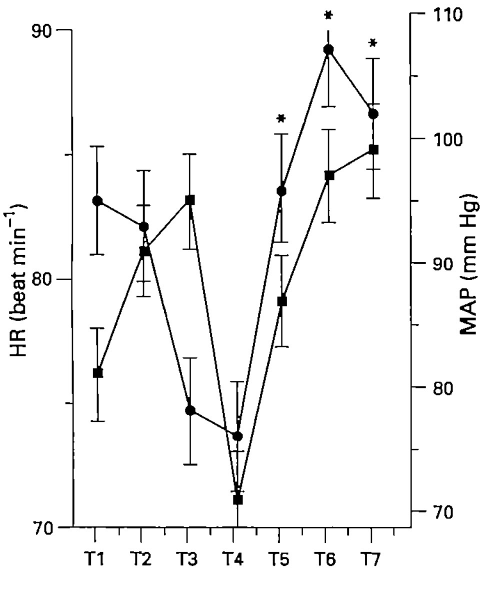


Figure 1 Mean (SD) changes in heart rate (HR) (■) and mean arterial pressure (MAP) (●) 5 min before (T2) and 5 min after (T3) induction, 5 min before (T4) and 5 min after (T5) insufflation of carbon dioxide, 5 min after reverse Trendelenburg positioning (T6) and after exsufflation of carbon dioxide (T7). T1 = Baseline. Significant difference ($^*P < 0.05$) in MAP from T4 to T5, T6 and T7.

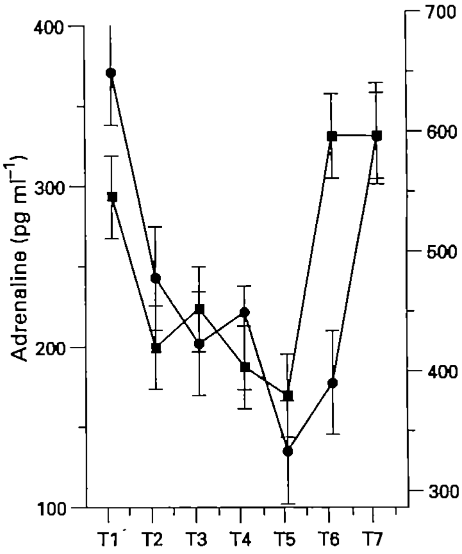


Figure 2 Mean (SD) changes in plasma concentrations of adrenaline (■) and noradrenaline (●). Times T1–T7 as in figure 1.

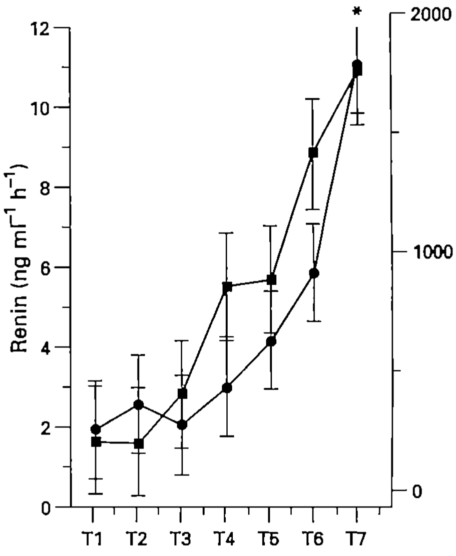


Figure 3 Mean (SD) changes in plasma concentrations of renin (■) (normal range 0.5–4.2 ng ml^{-1} h^{-1}) and aldosterone (●) (normal range 30–1000 pg ml^{-1}). Times T1–T7 as in figure 1. Significant difference ($^*P < 0.05$) in: plasma renin from T1, T2 and T3 to T7; plasma aldosterone from T1, T2, T3, T4, T5 and T6 to T7.

Plasma concentrations of renin increased four-fold during changes in position but this was not significant ($P = 0.31$). This increase continued after exsufflation of carbon dioxide and reached statistical significance ($P = 0.005$). Similarly, plasma concentrations of aldosterone increased four-fold after reverse Trendelenburg positioning but was not significant. The increase continued during exsufflation and achieved statistical significance ($P = 0.0001$) (fig. 3).

There was a linear increase in plasma prolactin concentrations after induction of anaesthesia. This became significant before insufflation of carbon

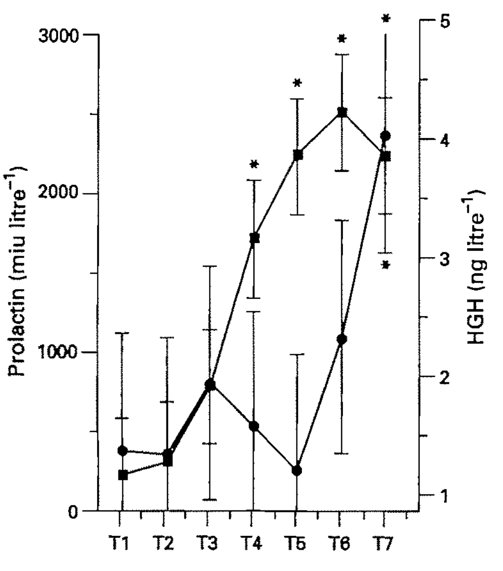


Figure 4 Mean (SD) changes in plasma concentrations of human growth hormone (HGH) (●) and prolactin (■) (normal range 50–300 miu litre^{-1}). Times T1–T7 as in figure 1. Significant difference ($*P < 0.05$) in: prolactin from T1 to T4, T5, T6 and T7; HGH from T1, T2, T3 and T4 to T7.

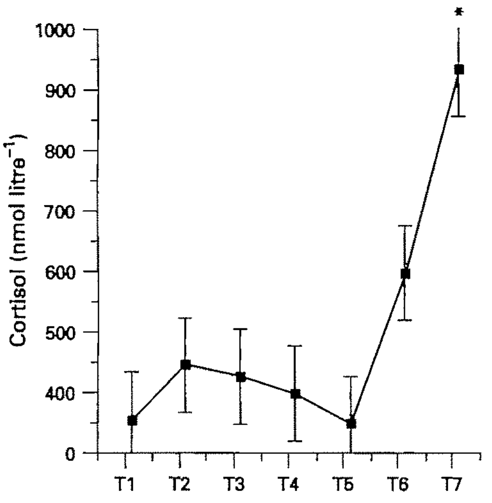


Figure 5 Mean (SD) changes in plasma concentrations of cortisol (normal range 300–700 nmol litre^{-1}). Times T1–T7 as in figure 1. $*P < 0.05$ compared with T1, T2, T3, T4, T5 and T6.

dioxide ($P = 0.003$) and remained increased for the rest of the study. Human growth hormone remained relatively stable after induction of anaesthesia and showed a significant increase after exsufflation of carbon dioxide ($P = 0.01$) (fig. 4).

Plasma concentrations of cortisol increased threefold after exsufflation of carbon dioxide ($P = 0.0002$) (fig. 5).

There was a linear correlation between changes in MAP and plasma concentrations of renin and aldosterone ($r = 0.97$ and 0.85, respectively) after pneumoperitoneum and reverse Trendelenburg positioning.

Discussion

The sequential effects of anaesthesia, positioning (20° reverse Trendelenburg), and mechanical and neuroendocrine effects of pneumoperitoneum and absorbed carbon dioxide combine to produce a characteristic haemodynamic response [4]. A biphasic pattern of initial reduction in cardiac index with subsequent recovery after pneumoperitoneum has been described [4]. In this study, we demonstrated that peritoneal insufflation of carbon dioxide to an intra-abdominal pressure of 14 mm Hg induced characteristic increases in MAP but no acute ECG ST segment changes in a series of healthy, non-obese patients, free from cardiac disease, undergoing elective laparoscopic cholecystectomy.

In patients with mild heart disease or those with clinically severe systemic disease (ASA III–IV), the pattern of changes in cardiac index, MAP and SVR is qualitatively similar to that observed in series of healthy patients [9–11]. The most striking features are the considerable initial reductions in cardiac index occurring simultaneously with large increases in MAP and SVR, followed by recovery of cardiac index, as described in healthy patients. This study suggests that acute haemodynamic changes during pneumoperitoneum and changes in position in healthy patients do not provoke ECG ST segments changes characteristic of myocardial ischaemia. Such changes were observed in only two patients, in one case associated with an episode of hypotension and bradycardia after induction of anaesthesia and in the other during peritoneal exsufflation.

Continuous ambulatory electrocardiographic (CAECG) monitoring has been developed as a non-invasive method of detecting perioperative myocardial ischaemia [12]. A variety of independent measures of ischaemia, including abnormalities of myocardial perfusion, regional left ventricular dysfunction, and pulmonary and left ventricular changes have been correlated with transient ST segment changes [13]. Little information is available, however, on the diagnostic accuracy of CAECG monitoring in patients with no known history of coronary heart disease, especially in those patients with a relatively low pre-test probability of the disease [12]. Studies in normal subjects without coronary artery disease (CAD) have demonstrated a very low incidence of such ECG changes. Current consensus does not support the use of continuous ST segment monitoring as a screening tool for detecting CAD [12]. In our series of 16 patients, free from cardiac disease, only one patient developed acute ST segment changes during deflation of the pneumoperitoneum. There were no postoperative sequelae, as detected by clinical assessment, serial ECG and cardiac enzymes.

The effects of abdominal distension with carbon dioxide are complex and may combine direct mechanical compressive effects, neurohumoral responses and changes induced by the absorbed carbon dioxide. Possible mediators of the initial and delayed changes in CI, MAP and SVR observed in this and other studies include catecholamines, prostaglandins, the renin–angiotensin system and vasopressin [5]. Joris and Lamy [8] documented significant vasopressin release after pneumoperitoneum that paralleled the time course of the increase in SVR. In this study, plasma concentrations of adrenaline, renin–aldosterone and prolactin increased considerably after pneumoperitoneum and change in position. Of particular importance was the time course of the increase in renin–aldosterone. The plasma concentration–time course profile of renin–aldosterone paralleled that of changes in MAP, suggesting a possible cause–effect relationship. Increased abdominal pressure associated with pneumoperitoneum may reduce venous return, compress the abdominal capacitance vessels, reduce cardiac output and renal blood flow. These factors may combine to activate the renin–aldosterone system. Even though prolactin increases in response to stress, the time course of its changes suggests an interaction with the opioid fentanyl [14]. The peak HGH and cortisol responses reflect the postoperative stress response and parallel the ischaemic experience in patient No. 8.

Considerable systemic absorption of carbon dioxide occurs during prolonged insufflation [15]. Hypercapnia may contribute to the delayed recovery of cardiac index and may attenuate the adverse haemodynamic affects of intra-abdominal pressure. Hypercapnia may also contribute to the documented changes in MAP and plasma concentrations of adrenaline observed in this and other studies [16, 17]. Deflation of the induced pneumoperitoneum is associated with acute increases in plasma concentrations of noradrenaline and cortisol. These may be secondary to a combination of factors, including the drugs used in reversal, the patient's return to consciousness or as a result of the patient experiencing pain.

References

1. Cunningham AJ, Turner J, Rosenbaum S, Raftery T. Transoesophageal echocardiographic assessment of haemodynamic function during laparoscopic cholecystectomy. *British Journal of Anaesthesia* 1993; **70**: 621–625.
2. Critchley LA, Critchley JAJH, Gin T. Haemodynamic changes in patients undergoing laparoscopic cholecystectomy: measurement by transthoracic electrical bioimpedance. *British Journal of Anaesthesia* 1993; **70**: 681–683.
3. Cunningham AJ, Brull SJ. Laparoscopic cholecystectomy: anesthetic implications. *Anesthesia and Analgesia* 1993; **76**: 1120–1133.
4. Wahba RWM, Beique F, Kleiman SJ. Cardiopulmonary function and laparoscopic cholecystectomy. *Canadian Journal of Anaesthesia* 1995; **42**: 51–63.
5. Joris JL, Noirot PN, Legrand MJ, Jacquet NJ, Lamy ML. Hemodynamic changes during laparoscopic cholecystectomy. *Anesthesia and Analgesia* 1993; **76**: 1067–1071.
6. Joris J, Cigarini I, Legrand M, Jacquet N, de Groote D, Franchimont P, Lamy M. Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy. *British Journal of Anaesthesia* 1992; **69**: 341–345.
7. Felber AR, Blobner M, Goegler S. Plasma vasopressin in laparoscopic cholecystectomy. *Anesthesiology* 1993; **V79**: A32.
8. Joris J, Lamy M. Neuroendocrine changes during pneumoperitoneum for laparoscopic cholecystectomy. *Clinical Circulation* 1992; A33.
9. Safran D, Sgambati S, Orlando R III. Laparoscopy in high-risk cardiac patients. *Surgery, Gynecology and Obstetrics* 1993; **176**: 548–554.
10. Fox LG, Hen HAT, Gawey BJ, Helman CL, Ramsay MAE. Physiologic alterations during laparoscopic cholecystectomy in ASA III and IV patients. *Anesthesiology* 1993; **79**: A55.
11. Iwase K, Takenaka H, Yagura A. Haemodynamic changes during laparoscopic cholecystectomy in patients with heart disease. *Endoscopy* 1993; **24**: 771–773.
12. Gottlieb SO. Detection of myocardial ischaemia using continuous electrocardiography. *International Anaesthesiology Clinics* 1992; **30**: 19–30.
13. Fleischer LA. Perioperative myocardial ischaemia and infarction. *International Anaesthesiology Clinics* 1992; **30**: 1–17.
14. Pan JT, Teo KL. Fentanyl stimulates prolactin release through mu-opiate receptors, but not the serotonergic system. *Endocrinology* 1989; **125**: 1863–1869.
15. Safran DB. Physiologic effects of pneumoperitoneum. *American Journal of Surgery* 1994; **167**: 281–286.
16. Rasmussen JP, Dauchot PJ, DePalma RG. Cardiac function and hypercarbia. *Archives of Surgery* 1978; **113**: 1196–1200.
17. Dhoste K, Karayan J, Lacoste L, Lehuede MS, Fusciardi J. Haemodynamic changes during laparoscopic cholecystectomy in the elderly. *British Journal of Anaesthesia* 1993; **72**: A32.

British Journal of Anaesthesia 1996; **76**: 645–651

Comparison of the effects of urapidil and sodium nitroprusside on haemodynamic state, myocardial metabolism and function in patients during coronary artery surgery

J. G. VAN DER STROOM, H. B. VAN WEZEL, I. VERGROESEN, J. E. KAL, J. J. KOOLEN,
J. P. DIJKHUIS, A. SWAAN, M. PORSIUS, H. A. J. KLEINJANS AND P. A. VAN ZWIETEN

Summary

We have compared, in an open randomized study, the effects of sodium nitroprusside (SNP) and urapidil on haemodynamic state and myocardial function and metabolism in two groups of patients undergoing elective coronary artery surgery. Sixty patients were allocated randomly to one of two groups: group SNP ($n = 29$) received SNP at an initial rate of 1–2 μg kg^{-1} min^{-1}; group URA ($n = 31$) received one or more bolus injections of urapidil 25 mg and an i.v. infusion at an initial rate of 11–21 μg kg^{-1} min^{-1}. Baseline measurements were obtained 10 min after introduction of an echotransducer into the oesophagus. Subsequently, vasodilator therapy was started in both groups. Infusion rates were adjusted to maintain systolic arterial pressure at 80–120% of baseline values (or mean arterial pressure < 100 mm Hg). Additional measurements were obtained 10 min after the start of vasodilator therapy and after sternotomy when the pericardium was opened. At each measuring time a complete haemodynamic profile, coronary sinus blood flow (CSBF) curves, transoesophageal echocardiographic images, and arterial and coronary venous blood samples were obtained. Arterial pressure was controlled adequately in both groups. After sternotomy, heart rate and cardiac index increased in both groups. At that time, there was a significant increase in myocardial oxygen consumption and CSBF in group URA ($P < 0.05$). However, the ratio between myocardial oxygen demand and oxygen supply remained unchanged and there was no difference in the number of ischaemic episodes between the groups (*Br. J. Anaesth.* 1996; **76**: 645–651).

Key words

Surgery, cardiovascular. Cardiovascular system, effects. Heart, myocardial function. Pharmacology, urapidil. Pharmacology, sodium nitroprusside.

Sodium nitroprusside (SNP) is a classic drug for the management of perioperative hypertension. However, SNP is known to induce several undesirable side effects, including reflex tachycardia, intrapulmonary and intracoronary shunting, tachyphylaxis and cyanide toxicity [1–4]. At present, calcium channel blockers, ketanserin and urapidil are common alternatives for the treatment of perioperative hypertension. Urapidil (URA) may be characterized pharmacodynamically as a selective α_1 adrenoreceptor antagonist causing a reduction in peripheral vascular resistance and hence a reduction in arterial pressure [5]. Additionally, it exerts an agonistic effect on central 5-HT$_{1A}$ receptors in the ventral medullary region [6–8]. Reflex tachycardia does not occur, probably as a result of reduced sympathetic outflow and vagal stimulation [9]. This pharmacodynamic profile suggests the possible usefulness of this agent in the management of patients with coronary artery disease (CAD) developing hypertension in the perioperative period.

Urapidil, administered i.v., has been shown to be effective for the control of arterial pressure in patients undergoing coronary artery surgery (CAS) [10, 11]. However, the effect of this agent on myocardial metabolism and coronary sinus blood flow (CSBF) in surgical patients is unknown. Therefore, in this study we compared the effects of urapidil and SNP on haemodynamic state, myocardial function, global myocardial metabolism and CSBF in patients undergoing CAS.

Patients and methods

After obtaining approval from the local Medical Ethics Committee and written informed consent, we studied 60 patients undergoing elective CAS. Exclusion criteria were patients with left ventricular (LV) end-diastolic pressure > 18 mm Hg, LV ejection fraction < 35%, atrioventricular conduction defects, unstable angina pectoris, severely impaired liver function (AST, ALT > 80 u. litre^{-1}), impaired renal function (men: creatinine > 110 μmol litre^{-1}; women: creatinine > 80 μmol litre^{-1}), acute rhythm

---

J. G. VAN DER STROOM, MD, H. B. VAN WEZEL, MD, PHD, J. E. KAL, MD, J. P. DIJKHUIS, MD, A. SWAAN, MD, M. PORSIUS, RN (Department of Anaesthesia); I. VERGROESEN, PHD (Department of Medical Physics); J. J. KOOLEN, MD, PHD, P. A. VAN ZWIETEN, MD, PHD (Department of Pharmacotherapy and Cardiology); Academic Medical Centre, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands. H. A. J. KLEINJANS, MD, Medical Department, Byk Nederland BV, Weerenweg 29, 1161 AG, Zwanenburg, The Netherlands. Accepted for publication: January 8, 1996.

Correspondence to J.G. van der S.

disturbances and those undergoing additional surgical procedures, such as valve replacement or aneurysmectomy.

Patients were allocated randomly to one of two groups: group SNP ($n = 29$) received SNP at an initial rate of 1–2 μg kg^{-1} min^{-1} and at a maximum maintenance infusion rate of 8 μg kg^{-1} min^{-1}; group URA ($n = 31$) received one or more bolus injections of urapidil 25 mg. In addition, urapidil was given at an initial infusion rate of 11–21 μg kg^{-1} min^{-1} and at a maximum maintenance infusion rate of 40 μg kg^{-1} min^{-1} [12]. All infusions were administered via a syringe pump. Polypropylene syringes and infusion cannulae were used throughout. Yellow syringes and infusion cannulae were used for SNP, as this vasodilator undergoes rapid decomposition when exposed to light.

In the operating room, two peripheral infusions and an 18-gauge radial artery cannula were inserted during local anaesthesia. A triple-lumen thermodilution pulmonary artery catheter (Baxter) and a coronary sinus catheter (Wilton-Webster Laboratories, Altadena, CA, USA, type CCS-7U-90B) were introduced via the left subclavian vein. The coronary sinus catheter was advanced into the coronary sinus by means of imaging intensification, fluoroscopy and injection of contrast medium (Hexabrix), so that the external thermistor lay 1–1.5 cm from the ostium. The coronary sinus catheter was connected to a Wilton Webster Wheatstone bridge. Coronary sinus thermodilution signals were recorded with a multichannel amplifier/recorder system. Catheter calibration factors provided by the manufacturer were used. The absence of right atrial admixture in coronary sinus blood (coronary sinus reflex) was checked by injection of cold saline into the right atrium, while coronary sinus thermodilution curves were recorded simultaneously [13, 14]. Infusion rates were verified by timed volume collection, and flow calculations reflected the indicator infusion rate that was used.

All oral medication, with the exception of calcium antagonists, was continued until the morning before surgery. Lorazepam 4 or 5 mg orally, was given as premedication, 2 h before surgery. After preoxygenation, pancuronium 2 mg was given, followed by fentanyl 100 μg kg^{-1} i.v. over 3–5 min and midazolam 5 mg. When the patient became unresponsive to verbal commands an additional dose of pancuronium 6 mg was given; ventilation was assisted and then controlled manually. After intubation of the trachea, the lungs were ventilated with air–oxygen ($F\text{I}_{\text{O}_2} = 0.5$). Ventilation was adjusted to maintain the end-tidal carbon dioxide concentration at 4–4.5 %.

Baseline measurements (measurement I) were obtained at least 10 min after introducing an oesophageal echotransducer (5-MHz Hewlett–Packard omniplane or biplane, Boblingen, Germany). Subsequently, vasodilator therapy was started in both groups and a bolus of urapidil 25 mg i.v. was given in group URA. Infusion rates were adjusted to maintain systolic arterial pressure (SAP) at 80–120 % of baseline values. Furthermore, mean arterial pressure (MAP) was maintained less than 100 mm Hg at all times. Additional measurements were obtained 10 min after the start of vasodilator infusion (measurement II) and after sternotomy when the pericardium was opened (measurement III). At each measurement time, a complete haemodynamic profile, electrocardiographic tracing (leads II and V5), CSBF curves and transoesophageal echocardiographic (TOE) images (videotaped for off-line analysis) were obtained. CSBF was measured by continuous thermodilution [15]. Simultaneous blood samples were obtained from the radial artery and coronary sinus for measurement of oxygen tension and saturation, haemoglobin and whole blood lactate concentrations.

Cardiac output was measured by the single bolus thermodilution technique. Cardiac output measurements were repeated until three consecutive measurements with less than 10 % variability were obtained. Derived haemodynamic variables were calculated according to standard formulae. Oxygen saturation was measured by means of an OSM-II haemoximeter (Radiometer, Copenhagen) and $P\text{o}_2$ by an ABL-III (Radiometer, Copenhagen). Lactate concentration was measured using standard enzymatic techniques [16].

Myocardial metabolic indices were calculated according to standard formulae.

Arterial oxygen content ($C\text{a}_{\text{O}_2}$):

$$C\text{a}_{\text{O}_2}(\text{ml } 100 \text{ ml}^{-1}) = 1.39 \times \text{Hb} \times S\text{o}_2 + 0.003 \times P\text{o}_2$$

where Hb = haemoglobin (g 100 ml^{-1}), $S\text{o}_2$ = arterial oxygen saturation and $P\text{o}_2$ = arterial oxygen tension (kPa).

Myocardial oxygen supply ($M\text{o}_2$):

$$M\text{o}_2 \text{ (ml min}^{-1}) = C\text{a}_{\text{O}_2} \text{ (ml dl}^{-1}) \times \text{CSBF (ml min}^{-1})/100$$

Myocardial oxygen consumption ($M\dot{V}\text{o}_2$):

$$M\dot{V}\text{o}_2 \text{ (ml min}^{-1}) = \text{CSBF} \times (C\text{a}_{\text{O}_2} - C\text{c}_{\text{O}_2})$$

where $C\text{c}_{\text{O}_2}$ = coronary sinus oxygen content and $C\text{a}_{\text{O}_2}$ = arterial oxygen content.

Myocardial lactate extraction (MLE):

$$\text{MLE}(\%) = \frac{\text{lactate}_{\text{art}} - \text{lactate}_{\text{cs}}}{\text{lactate}_{\text{art}}} \times 100$$

Coronary vascular resistance (CVR):

$$\text{CVR (mm Hg ml}^{-1} \text{ min}^{-1}) = \frac{\text{MAP} - \text{RAP}}{\text{CSBF}}$$

where RAP = right atrial pressure.

TRANSOESOPHAGEAL ECHOCARDIOGRAPHY

Echocardiographic data were obtained with a standard Hewlett Packard 5-MHz omniplane or biplane phased array transducer. After tracheal intubation the echotransducer was introduced in the oesophagus and connected to a Hewlett–Packard Sonos 1500 echocardiograph. The transducer was positioned at the level of the papillary muscle. Cross-sectional echocardiograms were recorded on videotape at the measuring times mentioned above. Quantitative analysis of echocardiograms was performed using a computer-aided contouring system (Digisonics). The peak of the R wave of the simultaneously displayed electrocardiogram was used to select end-diastolic stop-frames. End-systolic stop-frames were defined as the minimal cross-sectional area of the left ventricle. End-diastolic and end-systolic areas were calculated. In all images the endocardial outlines were confirmed by playing through preceding and succeeding beats in real-time, slow motion and stop-frame format. The LV (left ventricular) percentage area reduction, defined as

$$\mathrm{PAR}(\%) = \frac{\text{diastolic area} - \text{systolic area}}{\text{diastolic area}} \times 100$$

was calculated using a floating axis analysis system [17, 18], and used as a variable characteristic for myocardial contractility. LV percentage area reductions in three consecutive heart beats were analysed and averaged. Endocardial contouring was performed by an experienced observer who was blinded to patient data. Regional myocardial function was assessed semi-quantitatively.

Electrocardiographic myocardial ischaemia was defined by a horizontal ST-T segment shift of at least 0.1 mV at 80 ms beyond the J point of at least 1 min duration. Myocardial ischaemia detected by echocardiography was defined as the occurrence of new regional wall motion abnormalities.

Myocardial lactate production was used as a metabolic marker of myocardial ischaemia.

Creatine phosphokinase isoenzyme MB (CK-MB) concentrations were measured immediately on arrival in the intensive care unit and at 3-h intervals during the first 9–12 h after operation. If there was still an increase in CK-MB concentrations after 12 h, additional measurements were performed at 3-h intervals until CK-MB concentrations decreased. The measurements were performed using radio-enzymatic techniques [19]. Myocardial infarction was diagnosed when CK-MB concentrations increased to > 70 u. litre^{-1}.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Wilcoxon, Mann–Whitney U test (two-sided) with a correction according to Bonferroni–Holm. $P < 0.05$ was considered significant. Results are reported as mean (SD).

Results

Before operation, the two groups of patients were comparable in age, weight, body surface area, left ventricular end-diastolic pressure, degree of coronary artery disease and oral medication (table 1).

We studied 60 patients. In nine patients no reliable coronary sinus thermodilution signal was recorded or coronary sinus blood sampling was impossible (group SNP, five patients; group URA, four patients). Data obtained at that time are not reported. In two patients urapidil was combined with SNP to obtain acceptable control of arterial pressure. Because of this combination of antihypertensive agents, the data obtained in these two patients are not reported. In two patients in group SNP, arterial pressure did not respond adequately. In these two patients, however, no additional antihypertensive therapy was used and therefore all data obtained in those patients were included in the final analysis.

Accordingly, the results of 24 patients treated with SNP and 25 patients treated with urapidil are described.

Table 1 Patient characteristics, degree of coronary artery disease and preoperative medication (mean (SD or range) or number). SNP = Sodium nitroprusside; URA = urapidil; BSA = body surface area

	SNP	URA
n	29	31
Age (yr)	60 (36–74)	58 (35–74)
Weight (kg)	76 (10.0)	81 (12.1)
BSA (m^2)	1.9 (0.2)	1.9 (0.2)
LVEDP (mm Hg)	13.2 (5.2)	12.4 (5.5)
Coronary artery disease (n)		
Single-vessel disease	1	0
Two-vessel disease	6	7
Three-vessel disease	22	24
Preoperative medication (n)		
β Adrenergic blockers	20	23
Long-acting nitrates	18	21
Ca^{2+} antagonists	21	23

Table 2 Mean (SD) infusion rates and duration of infusion in the sodium nitroprusside (SNP) and urapidil (URA) groups

		Infusion rate (μg kg^{-1} min^{-1})		
Group	n	Drug + 10 min	Post-sternotomy	Duration of infusion (min)
SNP	24	1.2 (0.8)	1.4 (0.7)	59 (45)
URA	25	16.0 (8.8)	17.9 (11.9)	60 (47)

DOSES USED

The mean infusion rate administered during the first 10 min and after sternotomy are shown in table 2. Mean infusion rates during the entire study were 12.6 (6.6) μg kg^{-1} min^{-1} (range 4.8–34.6 μg kg^{-1} min^{-1}) for urapidil and 1.0 (1.0) μg kg^{-1} min^{-1} (0.1–2.6 μg kg^{-1} min^{-1}) for SNP. The mean total bolus dose of urapidil administered during the entire study was 98.2 (41.8) mg.

HAEMODYNAMIC VARIABLES

Measured and calculated haemodynamic variables at the three measuring times are shown in table 3. Baseline variables in the two groups were not significantly different. At measurement time II, both SAP and MAP decreased significantly in group URA while in group SNP only SAP decreased significantly compared with baseline. At measurement time III, SAP, DAP and MAP decreased significantly in group URA, and DAP and MAP decreased significantly in group SNP compared with baseline. MAP had to be titrated to less than 100 mm Hg. This could not be achieved in two patients in group SNP and in two patients in group URA.

Table 3 Mean (SD) haemodynamic changes in 60 patients receiving sodium nitroprusside (SNP) or urapidil (URA). Study periods were: I = baseline (before starting vasodilator therapy); II = 10 min after the start of drug infusion; III = after sternotomy when the pericardium was opened. SAP = Systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure; HR = heart rate; RAP = right atrial pressure; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; CO = cardiac output; CI = cardiac index; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; LVSWI = left ventricular stroke work index; RVSWI = right ventricular stroke work index; SVI = stroke volume index; SV = stroke volume. Significant differences ($P < 0.05$) compared with: *baseline; † study period II within group; ‡ study period I between groups

		Study period		
		I	II	III
SAP (mm Hg)	SNP	128.9 (20.5)	118.3 (19.9)*	118.3 (17.5)
	URA	131.0 (25.4)	118.4 (22.5)*	113.5 (25.0)*
DAP (mm Hg)	SNP	67.0 (12.7)	62.3 (11.4)	59.5 (10.9)*
	URA	68.3 (13.4)	62.0 (11.9)	58.6 (10.9)*
MAP (mm Hg)	SNP	87.7 (14.4)	81.0 (12.0)	79.7 (12.4)*
	URA	89.2 (16.6)	80.6 (15.2)*	77.0 (14.9)*
HR (beat min^{-1})	SNP	58.6 (9.1)	62.4 (8.5)	67.7 (11.4)*†
	URA	62.2 (12.6)	66.1 (16.4)	73.9 (16.8)*†
RAP (mm Hg)	SNP	7.4 (2.9)	7.3 (3.5)	7.5 (3.1)
	URA	7.4 (2.8)	7.3 (2.8)	6.6 (3.3)
Mean PAP (mm Hg)	SNP	18.1 (4.1)	16.7 (4.9)	16.8 (4.6)
	URA	15.8 (4.2)	15.4 (4.5)	15.8 (4.5)
PCWP (mm Hg)	SNP	12.9 (4.1)	11.9 (4.3)	11.8 (3.7)
	URA	11.0 (4.0)	11.1 (3.8)	10.4 (4.0)
CO (litre min^{-1})	SNP	4.7 (1.1)	5.5 (1.4)*	5.7 (1.5)*
	URA	4.7 (1.2)	5.6 (1.5)*	5.9 (1.7)*
CI (litre min^{-1} m^{-2})	SNP	2.5 (0.5)	2.9 (0.7)*	3.0 (0.7)*
	URA	2.4 (0.6)	2.9 (0.6)*	3.0 (0.8)*
SVR (dyn s cm^{-5}	SNP	1465.8 (544.4)	1160.7 (418.9)*	1127.3 (462.8)*
	URA	1466.2 (437.7)	1104.0 (350.8)*	1012.3 (312.7)*†
PVR (dyn s cm^{-5})	SNP	97.3 (60.3)	8.0 (55.8)*	81.9 (60.8)
	URA	87.2 (52.5)	63.6 (37.3)	71.3 (45.2)
LVSWI (gm m^{-1} beat^{-1})	SNP	43.6 (12.0)	44.1 (12.8)	40.6 (9.8)
	URA	41.7 (11.3)	42.6 (13.2)	38.5 (13.5)
RVSWI (gm m^{-2} beat^{-1})	SNP	6.0 (2.2)	5.9 (2.8)	5.6 (2.6)
	URA	4.6 (2.1)‡	5.0 (2.7)	5.3 (2.9)
SVI (ml beat^{-1} m^{-2})	SNP	43.3 (10.3)	47.2 (13.0)	44.9 (11.8)
	URA	40.1 (11.1)	45.5 (12.6)*	42.6 (12.5)†
SV (ml beat^{-1})	SNP	82.0 (21.9)	89.6 (28.3)*	85.5 (26.8)
	URA	77.9 (22.3)	88.7 (26.7)*	83.1 (26.7)

HR increased significantly at measurement time III in both groups compared with baseline and measurement time II. Compared with baseline, CI increased, while SVR decreased in both groups at both measurement times II and III.

CORONARY SINUS BLOOD FLOW AND MYOCARDIAL METABOLISM

Coronary dynamics and myocardial metabolic variables are shown in table 4. Baseline variables in the two groups were not significantly different. At measurement time III, CSBF and $M\dot{V}O_2$ increased significantly in group URA compared with baseline and time II. There was a significant difference between the groups in the increase in $M\dot{V}O_2$ between measurement interval I–II and measurement interval I–III.

In three patients in group SNP lactate extraction changed to production (table 5), in two patients after 10 min of vasodilator therapy (measurement II) and in one patient after sternotomy (measurement III). One of these patients developed regional wall motion abnormalities during the study and ECG changes after cardiopulmonary bypass. After operation, this patient developed elevated CK-MB concentrations, indicative of myocardial infarction. In one patient in group URA, lactate extraction changed to production. No regional wall motion abnormalities, ECG changes or elevated CK-MB concentrations were found.

ECHOCARDIOGRAPHY

Baseline variables in the two groups were not significantly different. PAR increased significantly at measurement times II and III compared with control values in both groups. In groups SNP and URA, PAR was 67 (10)% and 66 (7)%, respectively, at baseline. After 10 min of drug infusion, PAR increased ($P < 0.05$) to 69 (10)% and 69 (7)%, respectively. At measurement time III, PAR increased ($P < 0.05$) to 71 (8)% and 70 (7)% compared with baseline. Compared with baseline measurements regional wall motion abnormalities developed in one or more segments in one patient in group SNP. This patient developed a perioperative myocardial infarction (elvated CK-MB concentrations). In three patients in group URA wall motion abnormalities occurred but none of these patients developed a myocardial infarction in the perioperative period.

Table 4 Mean (SD) coronary haemodynamic variables and global myocardial metabolism in the sodium nitroprusside (SNP) and urapidil (URA) groups. Study periods were: I = baseline (before starting vasodilator therapy); II = 10 min after the start of drug infusion; III = after sternotomy when the pericardium was opened. CSBF = Coronary sinus blood flow: $M\dot{V}o_2$ = myocardial oxygen consumption; Cc_{O_2} = coronary sinus oxygen content; Ca_{O_2} = coronary arterial oxygen content; MLE = myocardial lactate extraction; (VR = coronary vascular resistance. Significant differences ($P < 0.05$) compared with: baseline; †study period II within groups; ‡study periods I–II between groups; §study periods I–III between groups

		Study period		
		I	II	III
CSBF (ml min^{-1})	SNP	109.0 (37.3)	106.2 (36.3)	116.7 (38.0)
	URA	104.1 (35.5)	115.8 (40.0)	138.4 (45.0)*†§
$M\dot{V}o_2$ (ml min^{-1})	SNP	14.7 (5.5)	14.1 (5.2)	15.2 (5.5)
	URA	13.5 (5.4)	14.9 (5.8)‡	17.8 (6.7)*†§
Ca_{O_2} (ml dl^{-1})	SNP	19.9 (1.5)	19.9 (1.5)	19.9 (1.5)
	URA	20.4 (1.8)	20.4 (1.7)	20.4 (1.7)
Cc_{O_2} (ml dl^{-1})	SNP	6.4 (1.3)	6.6 (1.3)	7.0 (1.3)
	URA	7.5 (1.7)	7.6 (1.4)	7.6 (1.5)
MLE (%)	SNP	30.0 (9.9)	27.1 (16.2)	21.1 (22.9)
	URA	30.6 (16.9)	30.6 (19.9)	28.8 (14.4)
CVR (mm Hg ml^{-1} min^{-1})	SNP	0.8 (0.3)	0.8 (0.4)	0.7 (0.3)
	URA	0.9 (0.3)	0.7 (0.2)*	0.6 (0.2)*†§

Table 5 Ischaemic events during the study (number of patients) in the sodium nitroprusside (SNP) and urapidil (URA) groups

	SNP	URA
ST segment changes (leads II and V5)	0	0
Wall motion abnormalities	1	3
Myocardial lactate production	3	1
Myocardial infarction (CK-MB > 70 u. $litre^{-1}$)	3	0

ELECTROCARDIOGRAPHY

In one patient in group SNP ischaemia developed (ST segment depression in leads II and V5) followed by ventricular fibrillation during weaning from cardiopulmonary bypass (not during the study). This condition was treated successfully with electrical defibrillation (200 W s^{-1}) followed by continuous infusion of lignocaine. In this patient there was already a change from lactate extraction to production at measurement time II, as described above. We observed elevated CK-MB concentrations after operation in this patient (144 u. $litre^{-1}$).

In one patient in URA group there were signs of ischaemia on the ECG associated with hypotension. This condition occurred after cardiopulmonary bypass (not during the study) and disappeared during treatment with nitroglycerine and nicardipine. It seems therefore that coronary spasm had occurred, which was relieved by these vasodilators. In this patient CK-MB concentrations were within normal limits after operation.

CK-MB CONCENTRATIONS

The groups were comparable in duration of aortic cross-clamping (SNP 61 (10) min, URA 59 (9) min). Three patients in group SNP (table 5) developed a myocardial infarction, compared with none in group URA (ns). There were no significant differences between the groups in CK-MB concentrations in the first 12 h after operation.

Discussion

Hypertension, associated with increases in systemic vascular resistance, cardiac filling pressures and HR, frequently develops in patients undergoing CAS, particularly after sternotomy [20–22]. This type of hypertension probably results from activation of the sympathetic nervous system.

Urapidil is a relatively short-acting peripheral α_1 adrenoceptor blocker with an additional stimulating effect on central serotonin $(5\text{-HT})_{1A}$ receptors located in the ventral medullary region [7,23]. The importance of 5-HT receptors and pathways in the central regulation of arterial pressure has been substantiated by the discovery that central 5-HT_{1A} receptors, when stimulated with an appropriate agonist, mediate inhibition of peripheral sympathetic activity and a reduction in HR [8,24,25]. Reflex tachycardia associated with the use of urapidil has not been reported, probably as a result of reduced sympathetic activity and enhanced parasympathetic outflow [9,26]. This pharmacodynamic profile suggests the potential usefulness of urapidil in the management of patients with coronary artery disease (CAD) developing hypertension in the perioperative period [10].

In this study, it was not surprising to find a significant increase in HR in patients treated with SNP. However, patients treated with urapidil also developed tachycardia. Similar increases in HR were reported in patients with CAD given nifedipine, nicardipine or placebo for the treatment of hypertension after sternotomy [21,27,28]. In contrast with our findings, we reported previously that the use of urapidil given after operation, was not associated with significant changes in HR. This was confirmed by several investigators [11,29]. From these combined observations it appears likely that sympathetic activation after sternotomy is more pronounced than stimulation of the sympathetic system after operation. This may (partially) explain the increase in HR found in both groups.

Although urapidil has an inhibiting effect on sympathetic activity there is no published evidence that it has any negative inotropic properties. Wouters and colleagues described the absence of myocardial depression by urapidil in dogs with chronically ischaemic hearts [30]. Lepage and co-workers used radionuclide angiography to demonstrate that urapidil i.v. had no detectable negative inotropic activity in conscious patients with CAD and hypertension [31]. In a study in hypertensive patients after CAS, van der Stroom and colleagues demonstrated that urapidil was an effective and safe antihypertensive agent; its use was associated with a significant increase in PAR [12]. In this study, echocardiographic PAR also increased significantly and to a similar extent in both groups. The changes in PCWP and SVR, reflecting preload and afterload respectively, were of the same order of magnitude in both groups throughout the study. Consequently, our finding that both urapidil and SNP can increase PAR implies that these agents do not exert a relevant reduction in myocardial contractility.

For a better understanding of the changes in CSBF and $M\dot{V}O_2$ reported here, it is important to realize that regulation of coronary blood flow is primarily governed by local metabolic demand (i.e. metabolic flow regulation) [32]. From animal experiments it is known that within each experiment $M\dot{V}O_2$ and coronary oxygen supply are correlated, with an average slope of 1.3–1.6 [33].

Figure 1A shows that SNP did not change $M\dot{V}O_2$ substantially. The ratio of oxygen supply and demand remained normal (i.e. 1.35) and was not changed by the dose of SNP administered. This implies that SNP (in the doses used) did not have a direct coronary vasodilator effect, as all changes in oxygen supply can be attributed to a concomitant change in $M\dot{V}O_2$. This is in keeping with previous studies in patients undergoing CAS, which demonstrated that effective treatment of hypertension with SNP is not associated with changes in CSBF or $M\dot{V}O_2$ [21, 27].

In patients given urapidil, there appeared to be a trend towards the upper right corner (fig. 1B), implying a higher level of $M\dot{V}O_2$ and oxygen supply respectively. This appeared particularly prominent at the time of the highest infusion rate of urapidil, after sternotomy. This increase in $M\dot{V}O_2$ is difficult to explain. Of the determinants of $M\dot{V}O_2$, only HR increased significantly in both groups URA and SNP. Therefore, tachycardia can only partly explain this unexpected finding, as there was no change in $M\dot{V}O_2$ in group SNP. However, in the majority of patients given urapidil, the increase in $M\dot{V}O_2$ was adequately compensated by an increase in coronary oxygen supply, presumably because of metabolic flow regulation. An additional factor may be that block by urapidil of α_1 adrenoceptors in the coronary arterial wall, contributed to the increase in CSBF. Such a mechanism would explain the larger oxygen supply–demand ratio (1.35 for SNP and 1.56 for urapidil) and may also play a role in the absence of serious coronary adverse events in the presence of high levels of $M\dot{V}O_2$.

In summary, this study indicates that in the doses used, urapidil was equally effective and safe as SNP in controlling hypertension during CAS. Although the use of both agents resulted in tachycardia, only urapidil increased $M\dot{V}O_2$. This was associated with an increase in CSBF, without changes in the myocardial oxygen supply–demand ratio.

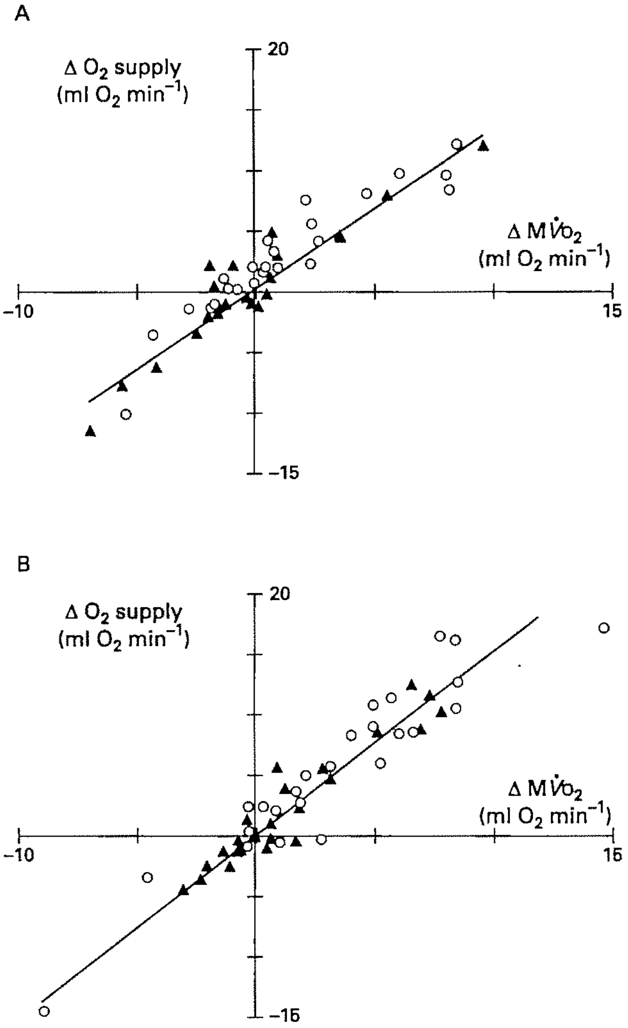


Figure 1 Relationship between oxygen supply (CSBF × Ca_{O_2}) and oxygen demand ($M\dot{V}O_2$) in anaesthetized patients undergoing coronary artery surgery. To be able to estimate the oxygen demand–supply ratio without the influence of the variation in intercepts caused by variation in coronary perfusion pressure and heart weights, the different (Δ) in $M\dot{V}O_2$ and oxygen supply between measurement II and control, and measurement III and control, are plotted for both sodium nitroprusside (SNP) (A) and urapidil (B). ▲ = Difference between measurement II (10 min of drug infusion) and measurement I (baseline) ($r^2 = 0.87$, $y = 1.35x$ for SNP; $r^2 = 0.90$, $y = 1.57x$ for urapidil); ○ = difference between measurement III (post-sternotomy) and measurement I (baseline) ($r^2 = 0.84$, $y = 1.35x$ for SNP; $r^2 = 0.87$, $y = 1.55x$ for urapidil).

Acknowledgement

Supported by a grant from Byli Nederland BV.

References

1. Palmer RF, Lasseter KC. Drug therapy. Sodium nitroprusside. *New England Journal of Medicine* 1975; **292**, 294–297.
2. Cohn, JN, Franciosa JA. Vasodilator therapy of cardiac

failure: (first of two parts). *New England Journal of Medicine* 1977; **297**: 27–31.

3. Tinker JH, Michenfelder JD. Sodium nitroprusside: pharmacology, toxicology and therapeutics. *Anesthesiology* 1976; **45**: 340–354.
4. Vesey CJ, Cole PV. Blood cyanide and thiocyanate concentrations produced by long-term therapy with sodium nitroprusside. *British Journal of Anaesthesia* 1985; **57**: 148–155.
5. van Zwieten PA, de Jonge A, Wilffert B, Timmermans PB, Beckeringh JJ, Thoolen MJ. Cardiovascular effects and interaction with adrenoceptors of urapidil. *Archives Internationales de Pharmacodynamie et de Therapie* 1985; **276**: 180–201.
6. van Zwieten PA. Hybrid or multifactorial drugs in antihypertensive treatment. *Journal of Hypertension* 1990; **8**: 687–696.
7. van Zwieten PA. Pharmacologic profile of urapidil. *American Journal of Cardiology* 1989; **64**: 1D–6D.
8. Kolassa N, Beller KD, Sanders KH. Involvement of brain 5-HT_{1A} receptors in the hypotensive response to urapidil. *American Journal of Cardiology* 1989; **64**: 7D–10D.
9. Fozard JR, Mir AK. Are 5-HT receptors involved in the antihypertensive effect of urapidil? *British Journal of Pharmacology* 1987; **90**: 24.
10. Hess W, Schulte Sasse U, Tarnow J, Veit S. Comparison of phentolamine and urapidil in controlling acute intra-operative hypertension in patients subjected to coronary artery bypass surgery. *European Journal of Anaesthesiology* 1985; **2**: 21–27.
11. Downer J, Williams DJ, Major E, Morgan RJM, Lalor J. Urapidil in the treatment of hypertension: a comparison with sodium nitroprusside following coronary artery bypass surgery. In: Amery A, eds. *Treatment of Hypertention with Urapidil. Preclinical and Clinical Update.* London: Royal Society of Medicine Services Limited, 1986; 115–120.
12. van der Stroom JG, van Wezel HB, Koolen JJ, Visser CA, van Zwieten PA. Comparison of the effects of urapidil and nitroprusside on hemodynamics and myocardial function in hypertention following cardiac surgery. *Blood Pressure* 1994; **3**: 31–38.
13. Mathey DG, Chatterjee K, Tyberg JV, Lekven J, Brundage B, Parmley WW. Coronary sinus reflux; a source of error in the measurement of thermodilution coronary sinus flow. *Circulation* 1978; **57**: 778–786.
14. Koberstein RC, Pittman DE, Klocke FJ. Right atrial admixture in coronary venous blood. *American Journal of Physiology* 1969; **216**: 513–535.
15. Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJ. Measurement of coronary sinus blood flow by continuous thermodilution in man. *Circulation* 1971; **44**: 181–195.
16. Lamprecht W, Stein P, Heinz F, Lactate. In: Bregmeyer HU, eds. *Methoden der enzymatischen Analyse.* Weinheim: Verlag Chemie, 1974; 1729–1737.
17. Parisi F, Moynihan PF, Folland ED, Feldman CL. Quantitative detection of region left ventricular contraction abnormalities by two-dimensional echocardiography. II. Accuracy in coronary artery disease. *Circulation* 1981; **63**: 761–767.
18. Moynihan PF, Parisi AF, Feldman CL. Quantitative detection of regional left ventricular contraction abnormalities by 2-dimensional echocardiography: I. Analysis of methods. *Circulation* 1981; **63**: 752–760.
19. Fiolet JW, Willebrands AF, Lie KI, ter Welle HF. Determination of creatine kinase isoenzyme MB (CK-MB): comparison of methods and clinical evaluation. *Clinical Chimica Acta* 1977; **80**: 23–35.
20. Bovill JG, Sebel PS, Stanley TH. Opioid analgesics in anesthesia: with special reference to their use in cardiovascular anesthesia. *Anesthesiology* 1984; **61**: 731–755.
21. van Wezel HB, Bovill JG, Koolen JJ, Barendse GA, Fiolet JW, Dijkhuis JP. Myocardial metabolism and coronary sinus blood flow during coronary artery surgery: effects of nitroprusside and nifedipine. *American Heart Journal* 1987; **113**: 266–273.
22. Wynands JE, Wong P, Townsend GE, Sprigge JS, Whalley DG. Narcotic requirements for intravenous anesthesia. *Anesthesia and Analgesia* 1984; **63**: 101–105.
23. Kolassa N, Beller KD, Sanders KH. Evidence for the interaction of urapidil with 5-HT1A receptors in the brain leading to a decrease in blood pressure. *American Journal of Cardiology* 1989; **63**: 36C–39C.
24. van Zwieten PA, Blauw GJ, van Brummelen P. Serotonergic receptors and drugs in hypertension. *Pharmacology and Toxicology* 1992; **70**: S17–S22.
25. Ramage A. The mechanism of the sympathoinhibitory action of urapidil: role of 5HT1A-receptors. *British Journal of Pharmacology* 1991; **102**: 998–1002.
26. Gillis RA, Kellar KJ, Quest JA, Namath IJ, Martino Barrows A, Hill K, Gatti PJ, Dretchen K. Experimental studies on the neurocardiovascular effects of urapidil. *Drugs* 1988; **35** (Suppl. 6): 20–33.
27. van Wezel HB, Bovill JG, Visser CA, Koolen JJ, Janse MJ, Meijne NG, Barendse GA, Floor LM, Djamin R. Myocardial metabolism, catecholamine balance, and left ventricular function during coronary artery surgery: effects of nitroprusside and nifedipine. *Journal of Cardiothoracic and Vascular Anesthesia* 1987; **1**: 408–417.
28. van Wezel HB, Koolen JJ, Visser CA, Dijkhuis JP, Vergroesen I, Moulijn AC, Deen L. Antihypertensive and anti-ischemic effects of nicardipine and nitroprusside in patients undergoing coronary artery bypass grafting. *American Journal of Cardiology* 1989; **64**: 22H–27H.
29. Mollhoff T, van Aken H, Mulier JP, Muller E, Lauwers P. Effects of urapidil, ketanserin and sodium nitroprusside on venous admixture and arterial oxygenation following coronary artery bypass grafting. *British Journal of Anaesthesia* 1990; **64**: 493–497.
30. Wouters PF, Marcus MA, van Aken HK, van de Velde M, Miserez M, Deruyter HA, Mignolet K, Flameng W. Global and regional haemodynamic effects of urapidil in conscious dogs with chronic coronary artery occlusion. *European Journal of Anaesthesiology* 1994; **11**: 381–390.
31. Lepage JY, Pinaud M, Helias J, Malinovsky JM, Cozian A, Petitet A, Souron R. Acute effects of urapidil on left ventricular function in hypertensive patients: comparison with clonidine using radionuclide angiography. *British Journal of Anaesthesia* 1994; **72**: 638–642.
32. Moffitt EA, Sethna DH. The coronary circulation and myocardial oxygenation in coronary artery disease: effects of anesthesia. *Anesthesia and Analgesia* 1986; **65**: 395–410.
33. Vergroesen, I., Noble, MIM, Wieringa PA, Spaan JAE. Quantification of O_2 consumption and arterial pressure as independent determinants of coronary flow. *American Journal of Physiology* 1987; **252**: H545–H553.

British Journal of Anaesthesia 1996; **76**: 652–656

Kinetics of methaemoglobin and serum nitrogen oxide production during inhalation of nitric oxide in volunteers

J. D. YOUNG, J. W. SEAR AND E. M. VALVINI

Summary

Inhaled nitric oxide is used increasingly to treat pulmonary hypertension and ventilation/perfusion mismatching in seriously ill patients, but little is known of the pharmacokinetics of its two principal metabolites, methaemoglobin and nitrogen oxides (nitrates and nitrites). We have studied the changes in these metabolites in six healthy volunteers during and after 3 h inhalation of 100 volumes per million of nitric oxide. Mean nitric oxide uptake was 0.49 (SD 0.08) ml min^{-1} at standard temperature and pressure, corresponding to 74% of the inhaled dose. During inhalation, methaemoglobin increased monoexponentially with a time constant of 45.6 (11.1) min by 1.77 (0.47)% of total haemoglobin. Serum nitrogen oxides increased from 36.7 (7.6) to 124 (17) µmol $litre^{-1}$, with a time constant of 172 (91.4) min and a volume of distribution of 331 (104) ml kg^{-1}. The volume of distribution for methaemoglobin calculated from nitric oxide uptake and the increase in methaemoglobin, was, on average, 14.3% less than predicted blood volume, suggesting that most of the absorbed nitric oxide initially forms methaemoglobin. Serum nitrogen oxides declined initially after inhalation ceased but then increased to a second peak between 45 and 180 min later. The cause of the second peak was not determined. (*Br. J. Anaesth.* 1996; **76**: 652–656)

Key words

Gases non-anaesthetic. Pharmacology, nitric oxide. Blood, haemoglobin.

Inhaled nitric oxide is used increasingly to treat acute pulmonary hypertension and improve ventilation/perfusion relationships in critically ill adults and children [1–4]. A large proportion of the inhaled nitric oxide is absorbed [5–7]. Most absorbed nitric oxide probably combines with oxyhaemoglobin, which has an affinity for nitric oxide about 1500 times greater than its affinity for carbon monoxide [8], forming methaemoglobin and nitrates. Methaemoglobin is then converted back to haemoglobin by several intra-erythrocytic enzymes of which NADH–methaemoglobin reductase is the most important [9]. However, direct conversion of nitric oxide to nitrite and subsequent oxidation to nitrate is also possible in biological fluids [10], and nitric oxide can also combine with deoxygenated haemoglobin to form nitrosyl haemoglobin [11]. Nitrate, the final metabolite of nitric oxide by all of these pathways, accumulates during inhalation of nitric oxide [12]. Data on the handling and elimination of nitrates are sparse and little is known about the metabolism of inhaled nitric oxide. In this study, we have determined if all of the absorbed inhaled nitric oxide reacts with oxyhaemoglobin to form nitrates and methaemoglobin or if direct conversion to nitrate also occurs, and investigated the pharmacokinetics of the nitrate produced.

Subjects and methods

The study was approved by the local Ethics Committee, and all subjects gave informed consent. We studied six healthy male volunteers, aged 30–38 yr, weighing 67–105 kg. A 16-gauge cannula was inserted in a forearm vein and blood was obtained for baseline methaemoglobin, total haemoglobin and serum nitrate and nitrite concentrations, measured together as serum nitrogen oxides.

Subjects were fitted with a leak-free face mask connected to a non-rebreathing valve. Nitric oxide was stored as a mixture of 2000 volumes per million (vpm) in nitrogen (BOC Special Gases, Guildford, England) and mixed with medical grade air to achieve a final inspired concentration of 100 vpm. Mixed expired gas was collected in an in-line 10-litre mixing chamber. Inspired and mixed expired nitric oxide concentrations were measured with a chemiluminescence analyser (CLD 700AL, Eco Physics, Dürnten, Switzerland). Inspired minute volume was determined from a dry gas meter fitted to the inspiratory limb of the circuit. Subjects inhaled nitric oxide for 3 h and then room air. Venous blood was obtained before inhalation of nitric oxide and at 15, 30, 45, 60, 90, 120 and 180 min during inhalation of nitric oxide. Blood was also sampled 15, 30, 45, 60, 90, 120, 180, 240, 300, 540 and 1260 min after inhalation ceased. Subjects were asked to avoid

---

J. D. YOUNG, BM, FRCA, DM, J. W. SEAR, MB, BS, PHD, MA, FRCA, E. M. VALVINI*, MD, Nuffield Department of Anaesthetics, Radcliffe Infirmary, Woodstock Rd, Oxford OX2 6HE. Accepted for publication: November 21, 1995.

*Present address:

Mary Rankin Dialysis Unit, Middlesex Hospital, Mortimer St, London W1N 8AA.

processed meats on the day of the experiment as these may contain added nitrites; no other restrictions were placed on their diet or fluid intake.

Methaemoglobin and total haemoglobin concentrations were determined using an OSM3 co-oximeter (Radiometer, Copenhagen, Denmark). Blood samples for measurement of serum nitrogen oxides (nitrate and nitrite) were centrifuged at 3000 rpm for 15 min and the serum separated and stored at −20 °C for later analysis. Serum was deproteinized with zinc sulphate solution 30 mmol litre^{-1} before analysis and added to hot acidic vanadium (III) chloride which converted the nitrates and nitrites to nitric oxide. This was eluted in a stream of nitrogen and then analysed using chemiluminescence (CLD 700AL). The method is identical to that described by Brahman and Hendrix [13]. All analyses were performed in duplicate and the mean value used. The inter-sample coefficient of variation of the assay was 2% and the inter-day coefficient of variation 10%. Samples were analysed in random order. Data were analysed using an analysis/graphics package (Kaleidagraph, v3.0.2, Abelbeck Software) on an Apple Macintosh "Quadra 950". Results are given as mean (SD).

For each subject the inspired and expired nitric oxide concentrations and minute volume were corrected for temperature, ambient pressure and water vapour, and used to calculate nitric oxide uptake ($\dot{V}$NO) at STPD (standard temperature and pressure dry). Methaemoglobin production during inhalation of nitric oxide at a fixed inspired concentration follows simple first-order kinetics [14] and therefore the methaemoglobin concentration at time t can be described by the equation:

$$\text{Methaemoglobin concentration at time } t = B+A\times(1-e^{-t/\tau}) \quad (1)$$

where B = initial (baseline) methaemoglobin concentration (as a percentage of the total haemoglobin), A = plateau concentration of methaemoglobin above baseline that would be reached if inhalation continued for a long time (as a percentage of the total haemoglobin), and τ = time constant in minutes.

This equation was fitted to the methaemoglobin concentration results during inhalation of nitric oxide for each subject using least squares regression. This gave estimates of A and τ. If this equation is differentiated and solved for $t = 0$, the maximum rate of increase in methaemoglobin concentration is obtained. This is given by A/τ and corresponds to the rate of increase of methaemoglobin concentration in the absence of any elimination (i.e. the initial rate of increase of methaemoglobin concentration).

If the rate of production of methaemoglobin and its initial rate of increase are known, an estimate of blood volume can be obtained if it is assumed that all of the nitric oxide absorbed initially forms methaemoglobin:

$$\text{Estimated blood volume (litre)} = \frac{\text{Methaemoglobin production (g min}^{-1}\text{)}}{\text{Initial rate of increase in blood methaemoglobin (g litre}^{-1}\text{ min}^{-1}\text{)}}$$

Thus estimated blood volume is given by:

$$\frac{\dot{V}\text{NO}\times\tau}{1.39\times A} \quad (2)$$

where $\dot{V}$NO = nitric oxide uptake (ml min^{-1}), A is now expressed in grams of methaemoglobin per litre of blood and τ is as before; 1.39 is the affinity of haemoglobin for nitric oxide in millilitres of nitric oxide per gram of haemoglobin.

Mean uptake of nitric oxide and estimates for A and τ were substituted into this equation to give estimated blood volumes. These were compared with other estimates calculated from regression equations using the subjects' heights and weights. Two different equations were used [15, 16] and the mean of the estimates taken. Neither the regression equations nor the calculations based on nitric oxide uptake have a correction for the difference between central and peripheral packed cell volume.

The increase in serum nitrogen oxides during inhalation of nitric oxide could be described by an equation characterizing the behaviour of a one-compartment kinetic model. The volume of distribution was then calculated assuming all inhaled nitric oxide formed nitrogen oxides, and clearance calculated as the volume of distribution divided by the time constant.

Results

The mean inhaled nitric oxide concentration was 100.0 (3.9) vpm and the mean mixed exhaled nitric oxide concentration was 36.0 (5.8) vpm. Mean uptake of nitric oxide was 0.49 (0.08) ml min^{-1} STPD; there were no trends in uptake during the study in any subject. Inspired nitrogen dioxide concentrations (measured in the first subject only) were less than 0.25 vpm. The mean methaemoglobin concentration before inhalation of nitric oxide was 0.87 (0.04)%, and the baseline serum nitrogen oxide concentration was 36.7 (7.6) μmol litre^{-1}. Changes in methaemoglobin and serum nitrogen oxide concentrations during the study are shown in figure 1. The mean peak serum nitrogen oxide concentration was 124.2 (17.0) μmol litre^{-1} and the highest value recorded was 151.1 μmol litre^{-1} in subject No. 6. The

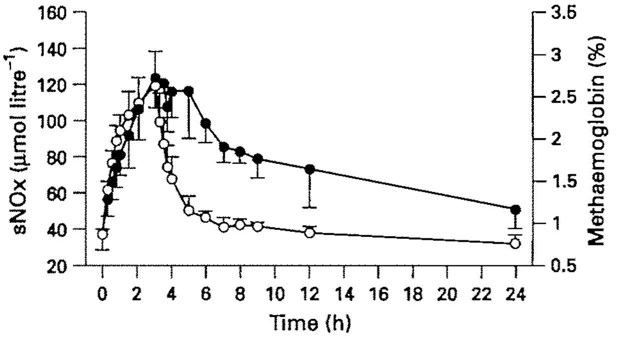


Figure 1 Change in serum nitrogen oxides (sNOx) (●) and methaemoglobin (○) in volunteers breathing inhaled nitric oxide 100 vpm (mean, SD). Nitric oxide was inhaled from 0 to 3 h.

Table 1 Uptake of nitric oxide and calculated results of methaemoglobin kinetics for all subjects during inhalation of nitric oxide

Subject No.	Height (cm)	Weight (kg)	Haemoglobin (g %)	Mean nitric oxide uptake (ml min^{-1} STPD)	τ (min)	*A* (% of total haemoglobin)	Estimated blood volume from regression equations (litre)	Estimated blood volume from nitric oxide uptake (litre)	Difference between estimates (%)
1	187	105	14.5	0.54 (0.07)	46.4	1.81	6.67	6.81	2.2
2	184	91	15.8	0.50 (0.04)	34.4	1.23	6.04	6.32	4.6
3	175	77	14.4	0.47 (0.07)	53.1	2.05	5.20	6.16	18.4
4	180	75	14.9	0.42 (0.01)	41.5	1.28	5.31	6.62	24.6
5	168	67	14.7	0.47 (0.05)	65.3	2.47	4.6	6.15	33.8
6	178	70	13.9	0.50 (0.07)	33	1.68	5.06	5.18	2.4
Mean (SD)				0.49 (0.08)	45.6 (11.1)	1.77 (0.47)			

Table 2 Calculated nitrogen oxide pharmacokinetic variables for all subjects during inhalation of nitric oxide

Subject No.	τ (minutes)	*A* (μmol litre^{-1})	Volume of distribution (litre)	Volume of distribution (ml kg^{-1})	Clearance (ml min^{-1})	Clearance (ml min^{-1} kg^{-1})
1	343	195	42.4	403	124	1.18
2	171	99	38.2	419	223	2.45
3	230	134	36.5	473	159	2.06
4	110	136	15.3	208	139	1.85
5	95	118	17.1	254	180	2.69
6	84	121	15.8	226	188	2.69
Mean (SD)	172 (91.4)	133 (29.9)	27.6 (11.6)	331 (104)	169 (32.7)	2.15 (0.53)

mean peak methaemoglobin concentration was 2.65 (0.46)% and the highest value was 3.3% in subject No. 5.

Serum nitrogen oxide concentrations showed a double "peak"; an initial peak at the end of inhalation of nitric oxide and a second peak which occurred in all subjects between 45 min and 3 h after cessation of inhalation of nitric oxide.

Table 1 shows the calculated results for methaemoglobin kinetics and blood volumes in all subjects. Blood volume calculated from uptake of nitric oxide was, on average, 14.3% higher than the value estimated from subjects' heights and weights. Table 2 gives the pharmacokinetic variables for nitrogen oxides for all subjects.

Discussion

In this study, two-thirds of the inhaled dose of nitric oxide was absorbed, somewhat less than would be expected from the results of other studies, where up to 95% of inhaled nitric oxide was absorbed during a breath-hold performed to measure the diffusing capacity of the lung for nitric oxide [6, 7]. The fraction of inspired nitric oxide absorbed varies between studies because the limiting factor for pulmonary absorption of nitric oxide is its pulmonary diffusing capacity and therefore uptake is a non-linear function of lung volume, respiratory timing and inspired concentration. The absorbed nitric oxide forms methaemoglobin and nitrates, and possibly a small amount of nitrosyl haemoglobin [11, 17]. It is not known if all of the absorbed nitric oxide initially forms nitrates and methaemoglobin, or if some of the inhaled nitric oxide either combines directly with water to form nitrites and subsequently nitrates [10] or transiently forms nitrosyl haemoglobin, which is converted rapidly to nitrogen oxides [18]. In a previous study to determine the kinetics of methaemoglobin production during inhalation of nitric oxide [14], the maximum rate of methaemoglobin production suggested that nearly all of the inhaled nitric oxide initially formed methaemoglobin, but no exhaled nitric oxide measurements were performed and all of the calculations were based on an assumed uptake of 80–90%. This study was performed with exhaled measurements to determine the fraction of adsorbed nitric oxide that reacts with haemoglobin to form methaemoglobin, and to determine the pharmacokinetics of the serum nitrogen oxides formed during inhalation of nitric oxide.

Measuring blood volume using inhaled gas was first attempted in 1882 [19] with a fixed volume of carbon monoxide and a single measurement of carboxyhaemoglobin; blood volume was assumed to be the same as volume of distribution of carboxyhaemoglobin. The technique we used to determine if nitric oxide initially forms methaemoglobin is essentially determination of volume of distribution of methaemoglobin using continuous inhalation of gas (equation (2) is a variation on the standard equation for calculating volume of distribution for an infused drug [20]). As methaemoglobin is entirely intravascular, this corresponds to blood volume. This technique requires a constant nitric oxide uptake, constant blood volume during nitric oxide inhalation, and that methaemoglobin elimination follows first-order kinetics. We have shown previously that methaemoglobin kinetics are both first order and linear in the range of concentrations studied here [14], that nitric oxide uptake was constant within subjects, and that blood volume would not be expected to change in the 3 h of the study. Ideally blood volume in the subjects should have been measured simultaneously with isotopically labelled red cells, but this was not possible. The agreement between the calculated and measured blood volumes suggests that the majority of the inhaled nitric oxide that is absorbed forms methaemoglobin, although in all cases blood volume calculated from nitric oxide uptake was greater than the expected value, and therefore 14% of the nitric oxide may have been absorbed without forming methaemoglobin. This could be by formation of nitrites and nitrates, or nitrosyl haemoglobin. When nitric oxide reacts with haemoglobin *in vitro*, the ratio of methaemoglobin to nitrosyl haemoglobin formation depends on oxygenation of haemoglobin; oxygenated haemoglobin forms methaemoglobin and nitrates whereas deoxygenated haemoglobin forms nitrosyl haemoglobin [11, 21]. As inhaled nitric oxide is absorbed into blood as it traverses the pulmonary capillary bed, it is reacting with haemoglobin that is 60–100% saturated, and therefore preferential formation of methaemoglobin would be expected. This has been confirmed by Wennmalm and colleagues [17] who could not detect nitrosyl haemoglobin in volunteers inhaling nitric oxide 25 vpm.

Baseline serum nitrogen oxide concentrations measured in this study were close to values reported previously [17, 22, 23]. In the only other published study of inhalation of nitric oxide and nitrates in humans, Wennmalm and colleagues [17] showed an increase in plasma nitrates 26 to 38 μmol litre^{-1} in volunteers inhaling 25 vpm for 1 h. In this study, at 1 h serum nitrogen oxide concentrations were 80.7 (10.7) μmol litre^{-1}, an increase of 44 μmol litre^{-1}. Volumes of distribution, clearances and time constants for serum nitrogen oxides were greater than values given in previous reports where oral doses of nitrate were given to volunteers. Wagner and coworkers [24] showed a volume of distribution of 21.1 litre, total clearance of 48.3 ml min^{-1} and elimination time constant of 429 min. Cortas and Wakid [23] reported nitrate clearance of 25.8 ml min^{-1}, and from their data the volume of distribution of the nitrate was approximately 19 litre and elimination time constant 740 min. These differences may reflect the different routes of administration; oral nitrates may have a different bioavailability than nitrates formed by inhalation of nitric oxide which is equivalent to an i.v. infusion. A reduced bioavailability of nitrates by the oral route would cause an apparent increase in the volume of distribution, but delayed absorbtion would explain the difference in clearances between our study and others. Clearance of nitrogen oxides in this study was close to the expected values for glomerular filtration rate, suggesting that nitrates are filtered but not reabsorbed in the kidney. The kidney is known to be a major elimination pathway for nitrates [24], and serum nitrates increased markedly in a patient with renal failure who received inhaled nitric oxide [12].

The calculated volumes of distribution and time constants assume a simple one-compartment model for nitrate handling. This may be an oversimplification. Although nitrate is a highly diffusible anion that would be expected to distribute throughout the whole body water, several short-term studies indicate this may not be the case. After oral nitrate loading, red cell nitrates are about two-thirds of plasma values [23], and tissue nitrate concentrations in rats given inhaled nitric oxide showed little increase after exposure [25]. Nitrates are probably actively excreted into saliva [18] against a concentration gradient. The volumes of distribution in our study and those cited above indicate a volume of distribution which is greater than the extracellular fluid volume but less than total body water, which is in agreement with the reported tissue to plasma nitrate gradient. The second peak in serum nitrogen oxides found in this study is also difficult to explain in terms of either one or multiple first-order processes. If all of the inhaled nitric oxide formed nitrates, when inhalation of nitric oxide ceased, serum nitrogen oxide concentration would decrease. One possible explanation for this second peak is the presence of a store of nitrogen oxides which are mobilized into the circulation some time after nitric oxide inhalation ceases. This may be related to the experimental procedure; subjects were seated during inhalation of nitric oxide but were free to walk around during the second stage of the experiment, which would both increase cardiac output and alter its distribution to different tissues. The anatomical site of this store of nitrogen oxides is unknown.

The inhaled concentration of nitric oxide used in these studies was greater than used clinically, where a maximum of 40 vpm is more common. The greater dose was used to ensure measurable changes within an acceptable time scale for a volunteer study.

In summary, we have demonstrated that the majority of inhaled nitric oxide reacts with haemoglobin producing methaemoglobin and nitrogen oxides, but up to 14% apparently undergoes direct conversion to nitrogen oxides. The nitrogen oxides produced have a volume of distribution of one-third of body weight and a clearance similar to glomerular filtration rate.

Acknowledgements

We thank Professor C. J. Hull for his valuable advice and help. The chemiluminescence analyser was purchased with a grant from the Wellcome Trust.

References

1. Roberts JD, Polaner DM, Lang P, Zapol WM. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet* 1992; **340**: 818–819.
2. Kinsella, JP, Neish SR, Shaffer E, Abman SH. Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet* 1992; **340**: 819–820.
3. Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *New England Journal of Medicine* 1993; **328**: 399–405.
4. Young JD, Brampton WJ, Knighton JD, Finfer SR. Inhaled nitric oxide in acute respiratory failure in adults. *British Journal of Anaesthesia* 1994; **73**: 499–502.
5. Wagner H-M. Absorption von NO und NO_2 in MIK- und MAK-konzentrationen bei der Inhalation. *Staub Rheinhalt Luft* 1970; **30**: 380–381.

6. Borland CDR, Higgenbottam TW. A simultaneous single breath measurement of pulmonary diffusing capacity with nitric oxide and carbon monoxide. *European Respiratory Journal* 1989; **2**: 56–63.
7. Guenard H, Varene N, Vaida P. Determination of lung capillary blood volume and membrane diffusing capacity in man by the measurement of NO and CO transfer. *Respiration Physiology* 1987; **70**: 113–120.
8. Gibson QH, Roughton FJW. The kinetics and equilibria of the reactions of nitric oxide with sheep haemoglobin. *Journal of Physiology (London)* 1957; **136**: 507–526.
9. Jaffe ER. Methaemoglobinaemia. *Clinics in Haematology* 1981; **10**: 99–122.
10. Ignarro LJ, Fukuto JM, Griscavage JM, Rogers NE, Byrns RE. Oxidation of nitric oxide in aqueous solution to nitrite but not nitrate: comparisons with enzymatically formed nitric oxide from L-arginine. *Proceedings of the National Academy of Science USA* 1993; **90**: 8103–8107.
11. Wennmalm A, Benthin G, Petersson A-S. Dependence of the metabolism of nitric oxide (NO) in healthy human whole blood on the oxygenation of its red cell haemoglobin. *British Journal of Pharmacology* 1992; **106**: 507–508.
12. Valvini EM, Young JD. Serum nitrogen oxides during nitric oxide inhalation. *British Journal of Anaesthesia* 1995; 74: 338–339.
13. Brahman RS, Hendrix SA. Nanogram nitrite and nitrate determination in environmental and biological materials by vanadium (III) reduction with chemiluminescence detection. *Analytical Chemistry* 1989; **61**: 2715–2718.
14. Young D, Dyar O, Xiong L, Howell S. Methemoglobin production in normal adults inhaling low concentrations of nitric oxide. *Intensive Care Medicine* 1994; **20**: 581–584.
15. Steinbeck AW. The plasma and blood volumes of normal Australasian males and notes on their estimation. *Australasian Journal of Experimental Biology* 1950; **28**: 477–485.
16. Wennesland R, Brown E, Hopper J jr, Hodges JL jr, Guttentag OE, Scott KG, Tucker IN, Bradley B. Red cell, plasma and blood volume in healthy men measured by radiochromium (Cr51) cell tagging and haematocrit: influence of age, somatotype and habits of physical activity on the variance after regression of volumes to weight and height combined. *Journal of Clinical Investigation* 1959; **38**: 1065–1077.
17. Wennmalm A, Benthin G, Edlund A, Jungersten L, Kieler-Jensen N, Lundin S, Westfelt UN, Petersson AS, Waagstein F. Metabolism and excretion of nitric oxide in humans. An experimental and clinical study. *Circulation Research* 1993; **73**: 1121–1127.
18. Yoshida K, Kasama K. Biotransformation of nitric oxide. *Environmental Health Perspectives* 1987; **73**: 201–206.
19. Grehant N, Quinquad E. Mesure de la quantite de sang contenu dans l'organisme d'un mammifiere vivant. *Journal de l'anatomie et de la physiologie normales et pathalogiques de l'homme et des animaux* 1882; **18**: 564–577.
20. Hull CJ. *Pharmacokinetics for Anaesthesia*. Oxford: Butterworth-Heinemann Ltd, 1991; 164–165.
21. Azoulay E, Lachia L, Blayo M-C, Pocidalo J-J. Methaemoglobin induced by nitric oxide in whole blood. Quantitative relationship. *Toxicological European Research* 1978; **1**: 7–12.
22. Evans T, Carpenter A, Kinderman H, Cohen J. Evidence of increased nitric oxide production in patients with the sepsis syndrome. *Circulatory Shock* 1993; **41**: 77–81.
23. Cortas NK, Wakid NW. Pharmacokinetic aspects of inorganic nitrate ingestion in man. *Pharmacology and Toxicology* 1991; **68**: 192–195.
24. Wagner DA, Schultz DS, Deen WM, Young VR, Tannenbaum SR. Metabolic fate of an oral dose of ^{15}N labeled nitrate in humans: effect of diet supplementation with ascorbic acid. *Cancer Research* 1983; **43**: 1921–1925.
25. Yoshida K, Kasama K, Kitabatake M, Okuda M, Imai M. Metabolic fate of nitric oxide. *International Archives of Occupational and Environmental Health* 1980; **46**: 71–77.

British Journal of Anaesthesia 1996; **76**: 657–662

Heart rate variability in patients recovering from general anaesthesia

N. IRELAND, J. MEAGHER, J. W. SLEIGH AND J. D. HENDERSON

Summary

We studied heart rate variability (HRV) using spectral analysis techniques in 58 adult patients recovering from general anaesthesia. The aim was to discover how HRV was affected by a variety of common preoperative, intraoperative and postoperative factors. ECG, respiration, level of consciousness, nausea, pain and arterial pressure were recorded during the first hour of recovery from general anaesthesia. HRV was found to decrease with increased weight, age, complexity of operation, use of reversal agents for neuromuscular block and preoperative beta-block. These effects were not mediated by changes in respiration. HRV was unaffected by administration of morphine. The level of nausea or pain had no effect on HRV except that pain decreased the relative ratio of high frequency to low frequency power within the power spectrum. In the group of patients that did not receive reversal agents, there was an abrupt increase in HRV when patients became responsive to verbal command. (*Br. J. Anaesth.* 1996; **76**: 657–662)

Key words

Anaesthesia, general. Heart, heart rate. Anaesthesia, depth. Memory. Recovery, postoperative.

Analysis of heart rate variability (HRV) has been used widely as a measure of activity in the sympathetic and parasympathetic components of the autonomic nervous system [1–3]. From oscillations in instantaneous heart rate, some information may be obtained on the status of the cardiovascular controlling systems. Spectral analysis of the R-R intervals is used commonly to quantify the components of beat-to-beat variability. The area under the power spectral curve in a particular frequency band is considered to be a measure of the variation in heart rate at that frequency.

From a variety of physiological experiments it has been demonstrated that inspiratory inhibition of vagal parasympathetic tone causes "high" frequency (HF) fluctuations in heart rate which are related to respiration. This effect seems to be mediated centrally via pathways between medullary respiratory and cardiovascular centres, and is well known as "respiratory sinus arrhythmia". The frequency of these oscillations depends on the breathing frequency but is usually 0.15–0.5 Hz. The origins of oscillations in the mid frequency (MF) (0.05–0.15 Hz) range are less well known but are thought to be caused mainly by the vasomotor part of the baroreflex arc [1]. Low frequency (LF) (< 0.05 Hz) fluctuations are believed to be largely the result of thermoregulatory changes in peripheral vascular resistance [1]. However, when HRV is measured in patients undergoing general or regional anaesthesia, the explanation of the observed changes is more difficult to interpret. It is certainly open to debate as to whether HRV is a reliable indicator of autonomic balance [4, 5], and how it is affected by respiration, anaesthetic drugs, illness and surgery [6–8].

Induction and maintenance of general anaesthesia cause a marked reduction in HRV [9, 10], and it has been proposed that monitoring HRV may provide a useful indicator of depth of anaesthesia [11]. All components of the HRV power spectra decrease with general anaesthesia and increase during the recovery period [9]. However, published studies have involved small numbers of patients who were not suffering from chronic diseases and were not receiving long-term medication. These factors have major effects on HRV and therefore may seriously limit its widespread application. With this in mind, an observational study was performed with the aim of understanding the clinical significance of the HRV power spectrum by recording sequential changes in HRV in a cross-section of patients awakening from general anaesthesia. Apart from documenting the changes in HRV that occur as the patient is awakening in the early recovery period, we hoped to identify factors that influence HRV, and study the associations of HRV data with adverse effects experienced during recovery from general anaesthesia. From this we also hoped to gain information on factors that influence the reliability of using HRV as an indicator of arousal and, possibly, awareness.

Patients and methods

DATA COLLECTION

After obtaining regional Ethics Committee approval and written informed consent, we studied 60 randomly selected hospital inpatients undergoing general

---

N. IRELAND, J. W. SLEIGH, MB, CHB, FRCA, DIPAPPSTATS (Department of Anaesthesia); J. MEAGHER, J. D. HENDERSON, PHD, MIEEE (Department of Physics); Waikato University, Hamilton, New Zealand. Accepted for publication: December 18, 1995.

Correspondence to J. W. S.

anaesthesia for a wide range of surgical procedures. Patients with known arrhythmias and those less than 16 yr of age were excluded. Information was recorded on clinical factors that were thought to possibly influence HRV. These included: preoperative data such as patient age, sex and weight, preoperative medications and significant clinical disease; intraoperative data such as type of surgery and anaesthetic drugs administered. The end of operation was defined as either the time when neuromuscular block was antagonized or when the anaesthetic vapour stopped if spontaneous respiration had been used. An attempt was made to grade the magnitude of surgery using the Resource Utilization System (RUS) score. This is a system that is used routinely in our hospital to grade the complexity of a particular operation for statistical purposes. It classifies operations on an ordinal scale of 1 (minor) to 4 (multiple major); postoperative data, including when the patient entered the recovery room, ECG, respiration and the patient's clinical state for the length of time that the patient was in the recovery room (minimum of 30 min) or until 1 h had elapsed.

ECG and respiratory data were recorded continuously, in serial "runs" of 300 R-R intervals. At the end of each run, the following clinical data were determined: (1) patient's level of consciousness (LOC) using the scale, 1 = alert and orientated, 2 = drowsy but rouses spontaneously, 3 = drowsy, arouses only to verbal command, 4 = asleep, arousable to stimulation, unarousable to verbal command and 5 = anaesthetized, unarousable to pain; (2) level of pain and nausea using the scale, 0 = none, 1 = mild, 2 = moderate and 3 = severe; (3) time of the patient's first response to a verbal command (the patient was requested to give a single hand squeeze) [12]; (4) medications administered and vital signs.

SIGNAL PROCESSING

The patient's ECG was obtained from lead II of a standard ECG monitor. This was fed to a 386DX computer fitted with a 12-bit Keithley DAS-1200 analogue/digital I/O board (Keithley, Taunton, MA, USA), where it was digitized using a sampling rate of 200 Hz. The signal was filtered digitally and processed to extract QRS peaks which determine the R-R intervals [13]. These peaks were then edited semi-manually to remove and interpolate ectopic beat artefacts. Spectral density was then determined by applying Welch's method to 100-s overlapping data segments which were weighted using the Bartlett window and fast Fourier transformed and averaged. Areas under the spectral density curve up to 0.50 Hz were determined by the trapezium rule. Low frequency (LF) (0.02–0.05 Hz), mid frequency (MF) (0.05–0.15 Hz) and high frequency (HF) (0.15–0.50 Hz) bandwidth powers were determined for each 300 R-R interval series.

The respiratory signal was obtained from a respiratory inductance plethysmograph (Respitrace, Studley Data Systems, Oxford). Data were sampled at 20 Hz by the Keithley board (12-bit) and stored on hard disk. The respiratory power spectrum was obtained in a manner identical to that of heart rate. The Respitrace was calibrated using a Wright's respirometer to obtain concurrent tidal volume readings of the first five breaths of the patient. We used the AC output from the Respitrace, without automatic resetting.

The influence of the lung volume signal on the HRV signal was estimated by multiplying the coherence function of the two spectra by the heart rate spectrum. This technique enables HRV power to be partitioned into a proportion that may be attributed to the lung volume signal and a component that is independent of the lung volume signal.

STATISTICAL ANALYSIS

We attempted to discover associations between the dependent HRV indices and the various explanatory "clinical" variables. These explanatory variables comprised preoperative, intraoperative and postoperative data, as described above.

HRV indices consisted of: (i) natural logarithms of absolute LF, MF, HF and total power (LFP, MFP, HFP, TotP); (ii) ratio of HF to LF and MF power (HF/LFMF); (iii) percentage power in each frequency band that could be attributed to respiration (%RHF, %RMF, %RLF, %RTot).

Because power spectral data commonly have a skewed distribution, we followed the example of Kato and colleagues [10] and performed a natural logarithmic transformation on the raw data. After checking for normality using Agostino's Omnibus-K^2 test [14], this allowed the use of parametric statistics for inter-individual comparison and Pearson's statistic for quantifying correlations between HRV indices. All HRV values in this article are therefore reported in $\ln\mathrm{BPM}^2$ units.

Statistical analyses were performed using the NCSS computer package (NCSS 5.01, Kaysville Utah). Initially, we performed an exploratory analysis of the data set looking for associations. The HRV indices were compared pairwise with the various clinical factors; visually using scatterplots and numerically using the Spearman rank correlation measure. Because three HRV power bands are compared with each explanatory variable, $P < 0.02$ was considered significant (giving an overall experimental type I error of $P = 0.056$). Using the NCSS package, it was possible to allow for the effect of other variables (so-called "partial" variables) on the correlation. This is similar to the use of covariates in ANCOVA models. The residual correlation between two variables is determined after a multiple linear regression has subtracted the effect of the partial variables. If the correlation coefficient is unchanged before and after the linear influence of the partial variables is removed, it is suggested that the partial variables are not confounding factors.

For those variables with a binary structure (such as whether or not the patient was receiving preoperative beta-blocker treatment), groups were compared using the *t* test.

From these results it was possible to build a multivariate model to attempt to account for the observed HRV using general linear model (GLM) multiple linear robust regression. The explanatory variables were the various clinical factors. This was done in a "forward stepwise selection" manner by sequentially adding variables to the model. To assess the potential power of HRV to predict wakefulness, a *post hoc* logistic regression was performed and the results presented as area under the receiver operating characteristic curve.

Results

We obtained 420 technically acceptable data records from 58 patients (table 1). Significant correlations between clinical variables and HRV indices are shown in table 2. It can be seen that the correlation coefficients were similar when respiratory-related HRV power was subtracted. This strongly suggests that the mechanisms by which the explanatory variables alter HRV are not mediated via respiratory changes. There was no single variable that was strongly correlated with any of the HRV indices.

The amount of HRV that could be accounted for by changes in lung volume was less than has been found in healthy volunteers, but varied widely between patients. The mean percentage of total power (%RTot) that was correlated with respiration was 46% (interquartile range 30–60%). In the low frequency band (%RLF) it was 43% (interquartile range 24–58%), in the medium frequency band (%RMF) 41% (28–51%) and in the high frequency band (%RHF) 56% (36–74%). The percentage of total power influenced by respiration did not change with increasing time from reversal ($P = 0.9121$).

Table 1 Patient data (mean (range) or number)

Age (yr)	54 (16–65)
Sex (M/F)	25/33
Preoperative disease	
Diabetes	4
Ischaemic heart disease	3
Preoperative medication	
Beta-blockers	11
ACE inhibitors	8
Thyroxine	5
Anaesthetic technique	
IPPV	33
Combined extradural–general anaesthesia	4
Propofol/thiopentone	40/18
Isoflurane/halothane	55/3
Suxamethonium/vecuronium/ pancuronium	2/22/5
Atracurium	6
Operation type	
Laparotomy	15
Thoracic	3
Urological	5
Vascular	4
Body surface	31

There were no significant differences between male and female groups for any of the HRV indices, but our results confirmed the well known negative correlation of HRV with increasing patient age. Of interest, there was a significant, and previously unreported, negative correlation of patient weight with all HRV indices. It appeared to be an independent factor. We repeated the correlation using other factors (age, beta-block, complexity of operation, use of reversal agents, LOC, pain and nausea) as partial correlates, but were unable to identify any confounding factors that might explain this observation. There was also a consistent negative correlation of all HRV indices with the complexity of operation, as estimated by the RUS score. Again, this was unaffected by age, beta-block, reversal agents, LOC, pain or nausea as partial correlates. Patients with diabetes had HRV indices that were low but not statistically different from non-diabetics. Patients who had a combined extradural–general anaesthetic technique had a higher mean TotP than those who received only general anaesthesia ($P = 0.042$).

DRUG EFFECTS

Beta-blocker use ($n = 11$) was associated with a significantly reduced TotP from a mean of 2.15 to 1.40 (SEM 0.12, $P = 0.0001$). This decrease was noted in all frequency bands, but was particularly marked in the MF band. This band also had the strongest negative correlation with beta-blocker use (table 2). Angiotensin converting enzyme (ACE) inhibitor use ($n = 6$) was associated with a slight increase in MFP from −0.10 to 0.58 (SEM 0.31, $P = 0.0197$), and a positive correlation between ACE inhibitor use and HF/LFMF ($r = 0.27$, $P = 0.0006$). There were no differences in HRV attributable to the different induction agents, volatile agents or neuromuscular blocking drugs. The use of reversal agents (neostigmine 2.5 mg and atropine 1.2 mg, $n = 33$) was associated with a significant decrease in HRV (TotP) from a mean of 2.43 to 1.70 (SEM 0.09, $P = 0.0001$). The difference was similar in all frequency bands. It was not possible to separate the effects of reversal

Table 2 Spearman correlation coefficients for respiratory and non-respiratory related HRV spectral power indices. Only correlations for $P < 0.02$ are shown. LF, MF and HF refer to the frequency bands 0.02–0.05, 0.05–0.15 and 0.15–0.5 Hz, respectively. The numbers in parentheses are the correlations after subtraction of the power that is correlated with changes in lung volume and thus is a measure of HRV power independent of respiration

	LFP	MFP	HFP	HF/LF
Age	−0.25 (−0.20)	−0.22 (−0.21)	0.28	
Weight	−0.24 (−0.23)	−0.26 (−0.28)	−0.31 (−0.32)	
Beta-block	−0.16 (−0.16)	−0.26 (−0.26)	−0.17 (−0.19)	
Reversal	−0.22 (−0.19)	−0.35 (−0.33)	−0.23 (−0.21)	
LOC	−0.17 (−0.17)	−0.17 (−0.16)	−0.21	−0.22
SAP	−0.23 (−0.23)	−0.12 (−0.12)	0.26	0.21
Heart rate	−0.22 (−0.29)	−0.13 (−0.20)	−0.22 (−0.26)	
RUS score	−0.17 (−0.17)	−0.19 (−0.24)	−0.17 (−0.18)	

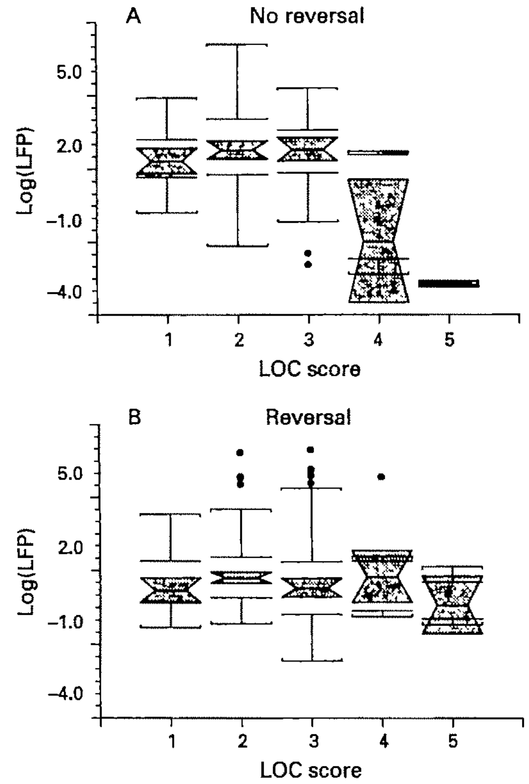


Figure 1 Box plots showing LFP *vs* LOC score in patients who did not have reversal (A) and in those who did (B). Central lines median of the group, with the "notches" showing the 95% confidence intervals of the median. Using this display, it is thus possible to make visual multiple comparisons for non-parametric significant differences between the groups. Outliers are shown as data points outside the (quartile ± 1.5 × interquartile range). Vertical axis is in $\ln BPM^2$ units.

agents from the use of neuromuscular blockers, or positive pressure ventilation, but it seemed likely that the observed effect was largely attributable to atropine.

There were no changes in HRV indices associated with morphine or metaclopramide administration during the recovery period.

PHYSIOLOGICAL CHANGES DURING RECOVERY

As shown in table 2, LOC had a significant negative correlation with LFP and MFP. This effect is shown in figure 1, which also demonstrates that the use of reversal agents eliminated the change in HRV power with LOC. In the group that did not receive reversal agents, there was a large increase in HRV power between LOC grades 3 and 4. This phenomenon occurred before and after patients became responsive to verbal command. If this is taken as a threshold level for consciousness, the area under the receiver operating characteristic curve was 0.91 in the non-reversed and 0.63 in the reversed group. We compared the predictive power of LFP with heart rate (HR) and systolic arterial pressure (SAP) alone, and in combination, using a logistic regression. Only LFP had values significantly different from zero. HR and SAP, either alone or in combination, could not distinguish between awake and asleep groups.

Pain had no significant effect on HRV indices, except for the HF/LFMF ratio which was decreased significantly ($r = -0.18$, $P = 0.02$). Nausea did not appear to have consistent effects on any of the HRV indices except to decrease HFP in the group that had not received reversal agents ($r = 0.21$, $P = 0.0007$).

Table 3 Pearson correlation coefficients among the HRV indices. All are significant ($P < 0.000$). The numbers in parentheses are the correlation coefficients for the subgroup of patients who were receiving beta-blockers

	MFP	HFP	TotP	HF/LFMF
LFP	0.82 (0.41)	0.70 (0.27)	0.96 (0.92)	−0.18
MFP		0.86 (0.69)	0.90 (0.64)	0.06
HFP			0.82 (0.52)	0.36
TotP				0.01

CORRELATIONS WITHIN HRV INDICES

The matrix of correlations between the various HRV indices is shown in table 3. In general the indices demonstrated strong linear correlations. However, as shown by the numbers in parentheses in table 3, the use of beta-blocking drugs appeared to be associated with a reduction in the correlation between the various indices. The use of reversal agents, ACE inhibitors, RUS score, LOC and pain or nausea score resulted in non-significant changes in the correlation coefficients.

MULTIVARIATE MODEL

Eight explanatory variables (age, weight, beta-block, RUS score, reversal, LOC, SAP and beta-block/SAP interaction term) were found to contribute significantly in a robust multiple linear regression model. This model achieved r^2 values of 56% for TotP, 52% for LFP, 63% for MFP and 43% for HFP. If the overall spectral power was partitioned by subtracting the power that was correlated with respiration (% Rtot) from TotP it was possible to derive the amount of spectral power that was independent of lung volume (NR-Tot). When a similar regression was performed, r^2 values of 47% were obtained for NR-Tot, and only 10% for % RTot. Thus about half of the variation in HRV can be accounted for using these predictor variables, none of which appears to act significantly via changes in respiration.

Discussion

This was a descriptive study and therefore interpretation of possible effects is difficult because of the problem of unknown confounding factors which may cause spurious correlations. Notwithstanding, there appeared to be several consistent observations. In this study, approximately 50% of this variability could be explained by a linear multivariate model using clinical variables. Presumably the rest of the interindividual variation was a result of other microscopic and biochemical changes that are not easy to measure. It is difficult to disentangle the relative effects of preoperative morbidity, residual effects of anaesthetic agents and activation of the surgical stress response. However, clearly HRV is correlated negatively with the complexity of the operation and weight of the patient. There is circumstantial evidence that stress hormonal activation may be an important modulator of HRV. Most studies have concentrated on the effects of the autonomic nervous system on HRV, but have ignored the fact that in situations of high sympathetic tone there are commonly coexisting elevations in vasopressin, renin, angiotensin II, corticosteroids and a number of autocoids controlling vasomotor tone [15, 16]. These hormones may act in at least two ways. Vasopressin is known to modulate directly the autonomic outflow from the brain stem by inhibiting vagal tone. Other substances may change peripheral resistance, thus affecting the oscillations in the HR feedback loops that manifest as LFP.

Pain (or nausea) does not appear to be associated with a marked increase in sympathetic power, as shown by an increase in the LFP and MFP bands. There are major problems with the common interpretation of MFP (or LFP) as being an indicator of sympathetic nervous system "tone" [17]. This explanation is based on changes in MFP induced by tilt or negative pressure studies in volunteers. In other hyper-adrenergic states (cardiac failure, exercise and high altitude hypoxia) there is a characteristic pattern in the HRV response, consisting of a decrease in LFP, increase in HR and a relative "switching off" of parasympathetic tone, as evidenced by a decrease in the HF/MFLF ratio. Saul and colleagues [18] compared HRV indices with sympathetic activity, as measured directly from the peroneal nerve, and by plasma noradrenaline concentrations. They found a marked heterogeneity in response. In 50% of their subjects there was a close association with LFP and muscle sympathetic nerve activity, but for the remainder there was no correlation.

Berger, Saul and Cohen [19] performed a canine study in which the cardiac sympathetic nerves were stimulated directly causing some increase in LFP but without effect on MFP. Furthermore, they demonstrated a decrease in LFP with increasing stimulation frequency. Malliani and colleagues [20] found that fluctuations in arterial pressure preceded variations in heart rate. We therefore conclude that it is more accurate to interpret MFP as an index of phasic (not tonic) sympathetic nervous system activity, principally mediated by oscillations in the baroreflex arc. The possible confounding effects of other stress hormones, such as angiotensin and vasopressin, are not mentioned in any of these studies. However, it is of interest to note that ACE inhibitors tend to increase HRV, particularly in the HF band. Hopf and colleagues [21] have compared HRV before and after preganglionic cardiac block using thoracic extradural local anaesthesia. They reasoned that if LFP was dependent on sympathetic activity, then block should result in a decrease in LFP. However, they found that absolute LFP did not decrease when the block was commenced but that HF/LF ratio did decrease with tilt, particularly if the cardiac nerves were not blocked. Interestingly, they reported an increase in vasopressin plasma concentrations in the presence of sympathetic block and tilt.

The effects of beta-block observed were depressant on all frequencies of HRV, but particularly inhibitory on phasic baroreflex activity (MFP). We also showed that beta-block appeared to have the effect of "uncoupling" the usually strong correlations between the different frequency bands in the HRV power spectrum. Beta-blockers have a number of pre- and postsynaptic actions that could affect HRV. Central beta-receptors are known to directly modulate vagal tone, in addition to causing dissociation of sympathetic neural traffic between different organs.

Our findings that LF and HF power are reduced with increasing depth of anaesthesia are consistent with similar studies [9, 10, 11, 22]. Kato and coworkers [10] made the important observation that the reduction in LF power is not related linearly to depth of anaesthesia, as measured by end-tidal volatile anaesthetic concentrations. We have obtained similar results using a relatively coarse clinical scale of arousal. As shown in figure 1, LFP (and HFP) increased abruptly in a stepwise manner at the point at which the patient became responsive to verbal command. This particular end-point may be an important clinical indicator of the possibility of awareness, or at least recall. Dutton, Smith and Smith [12] have studied patients recovering from general anaesthesia. They found that response to command was a useful indicator of anaesthetic depth, as evaluated by memory formation. In their study none of 22 patients who had a brief wakeful response to verbal command had memory formation. In contrast, 13 of 28 patients who could sustain wakefulness long enough to complete four hand squeezes on command had memory formation. On the scale that we used in our study, the transition from LOC grade 4 to 3 would correspond to Dutton's brief wakefulness level. Loss of amnesia starts to occur regularly at the transition from LOC grades 3 to 2. In our study HRV increased markedly when the patient moved from LOC grades 4 to 3. HRV is therefore a conservative marker of consciousness, increasing at the point at which there is a coordinated response to command, but relatively unrelated to the presence or absence of amnesia. We may conclude that a low HRV strongly suggests unawareness and furthermore an increase in HRV is a relatively early warning sign of conscious recall, the patient probably still being amnesic.

Our data tentatively suggest that HRV power may be a useful adjunct in monitoring depth of anaesthesia, but the findings need to be confirmed. In our *post hoc* analysis, if the patient had not received atropine, the LFP correctly categorized wakefulness in 92% of patients in our study. However, this result was biased because most of the patients were rousable by the time they were taken to the recovery area and therefore classified as being "awake". Further work needs to be done to establish accurately the true positive predictive value and appropriate threshold level of HRV. Nevertheless, even if it is not completely reliable, the use of HRV would seem to be a great improvement on the common clinical indicators of awareness. The discriminatory power to detect awareness was not improved if heart rate and systolic arterial pressure were included in the prediction. The predictive power also appeared to be relatively robust to many common medications and illnesses (ACE inhibition and opioids), but allowances in TotP of about -0.1 (lnBPM^2) per decade must be made for age and approximately -1 (lnBPM^2) for the use of beta-block. It was completely obtunded by the use of atropine.

Acknowledgement

We acknowledge funding from the Waikato Medical Research Foundation.

References

1. van Ravenswaaij CM, Kollee LA, Hopman JC, Stoelinga GB, van Geijn HP. Heart rate variability. *Annals of Internal Medicine* 1993; **118**: 436–447.
2. Pagani M, Lombardi F, Guzzetti S, Rimoloi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E, Turiel M, Baselli G, Cerutti S, Malliani A. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circulatory Research* 1986; **59**: 178–193.
3. Eckberg DL. Human sinus arrhythmia as an index of vagal cardiac outflow. *Journal of Applied Physiology* 1983; **54**: 961–966.
4. Higgins MS, Fleischer LA. A caution in the interpretation of heart rate variability data. *Anesthesia and Analgesia* 1994; **79**: 812.
5. Pagani M, Lombardi F, Malliani A. Heart rate variability: disagreement on the markers of sympathetic and parasympathetic activities. *Journal of the American College of Cardiologists* 1993; **22**: 951–952.
6. Landry DP, Bennett FM, Oriol NE. Analysis of heart rate dynamics as a measure of autonomic tone in obstetrical patients undergoing epidural or spinal anesthesia. *Regional Anesthesia* 1994; **19**: 189–195.
7. Galletly DC, Westenberg AM, Robinson BJ, Corfiatis T. Effect of halothane, isoflurane and fentanyl on spectral components of heart rate variability. *British Journal of Anaesthesia* 1994; **72**: 177–180.
8. Brown TE, Beightol LA, Koh J, Eckberg DL. Important influence of respiration on human RR interval power spectra is largely ignored. *Journal of Applied Physiology* 1993; **75**: 2310–2317.
9. Donchin Y, Feld JM, Porges SW. Respiratory sinus arrhythmia during recovery from isoflurane–nitrous oxide anesthesia. *Anesthesia and Analgesia* 1985; **64**: 811–815.
10. Kato M, Komatsu T, Kimura T, Sugiyama F, Nakashima K, Shimada Y. Spectral analysis of heart rate variability during isoflurane anesthesia. *Anesthesiology* 1992; **77**: 669–674.
11. Pomfrett CJD, Barrie JR, Healy TEJ. Respiratory sinus arrhythmia: An index of light anaesthesia. *British Journal of Anaesthesia* 1993; **71**: 212–217.
12. Dutton RC, Smith WD, Smith NT. Wakeful response to command indicates memory potential during emergence from general anaesthesia. *Journal of Clinical Monitoring* 1995; **11**(1): 35–40.
13. Pan J, Tompkins WJ. A real-time QRS detection algorithm. *IEEE Transactions on Biomedical Engineering* 1985; **32–3**: 230–236.
14. D'Agostino RB, Belanger A, D'Agostino RB jr. A suggestion for using powerful and informative tests of normality. *American Statistician* 1990; **4**: 316–321.
15. Tuominen HP, Svartling NE, Tikkanen IT, Saijonmaa O, Asko-Selijavaara S. Perioperative plasma endothelin-1 concentrations and vasoconstriction during prolonged plastic surgical proceedures. *British Journal of Anaesthesia* 1995; **74**: 661–665.
16. Piepoli M, Garrard ChS, Kontoyannis DA, Bernardi L. Autonomic control of the heart and peripheral vessels in human septic shock. *Intensive Care Medicine* 1995; **21**: 112–119.
17. Muzi M, Ebert TJ. Quantification of heart rate variability with power spectral analysis. *Current Opinion in Anesthesiology* 1993; **6**: 3–17.
18. Saul JP, Rea R, Eckberg DW, Berger RD, Cohen R. Heart rate and muscle sympathetic nerve variability during reflex changes of autonomic activity. *American Journal of Physiology* 1990; **258**: H713–H721.
19. Berger RD, Saul JP, Cohen R. Transfer function analysis of autonomic regulation I. Canine atrial response. *American Journal of Physiology* 1989; **256**: H142–H152.
20. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation* 1991; **84**: 483–492.
21. Hopf H-B, Skyschally A, Heusch G, Peters J. Low-frequency spectral power of heart rate variability is not a specific marker of cardiac sympathetic modulation. *Anesthesiology* 1995; **82**: 609–619.
22. Wang DY, Pomfrett CJ, Healy TE. Respiratory sinus arrhythmia: a new, objective sedation score. *British Journal of Anaesthesia* 1993; **71**: 354–358.

British Journal of Anaesthesia 1996; **76**: 663–667

Comparison of sedation with midazolam and ketamine: effects on airway muscle activity†

G. B. DRUMMOND

Summary

Male patients, aged 27–74 yr, without hypertension or overt cardiovascular disease were premedicated with temazepam 20 mg orally and allocated randomly to receive sedation with either midazolam (12 patients) in a dose sufficient to provide light sedation (retained response to loud voice) or ketamine 1 mg kg^{-1} (11 patients). Median midazolam dose was 0.08 (interquartile range 0.02) mg kg^{-1}. The activity of the muscles of the tongue, anterior neck and scalene group was measured with surface electrodes and compared with the awake state. Muscle activity decreased significantly after midazolam in each group of muscles, to median values of 42%, 28% and 33%, respectively, of awake values. Airway obstruction occurred in 10 of 12 patients and during obstruction muscle activity increased significantly to 69%, 73% and 52% of awake values, but in all cases this was insufficient to overcome the obstruction. After ketamine, activity did not change significantly and there were no episodes of airway obstruction. Phasic muscle activity was noted after sedation in 11 subjects but there was no difference in the incidence between the two groups (midazolam, six patients; ketamine, five patients). (*Br. J. Anaesth.* 1996; **76**: 663–667)

Key words

Hypnotics benzodiazepine, midazolam. Anaesthetics i.v., ketamine. Airway, muscles.

Sedation is used frequently in association with regional anaesthesia during surgery [1], and for procedures such as endoscopy [2]. Respiratory function is impaired frequently by sedation [3, 4] and sedation is associated with serious adverse events [5]. Sedative agents such as barbiturates [6] and benzodiazepines [7] cause loss of airway muscle tone and an increase in airway resistance [8]. Ketamine, which is a potential sedative for patients undergoing surgery with regional anaesthesia, appears to have less profound effects on the muscles of the upper airway [9]. In this study, we compared the effects of sedation with midazolam and ketamine on upper airway and respiratory muscles in men undergoing anaesthesia. Men were chosen as they seem to have more problems than women with airway patency in association with sedative use [10, 11]. We also investigated the effects of airway obstruction on airway muscle activity and the incidence of phasic patterns of activity of the muscles.

Subjects and methods

After obtaining approval from the local Ethics of Medical Research Committee and informed consent, we studied male patients undergoing routine surgical procedures under general anaesthesia. Patients were recruited if they had no overt cardiovascular or respiratory disease, and had a normal arterial pressure. Exclusion criteria were age more than 75 yr, body weight more than 120% of that expected for height and weight, obvious risk of regurgitation and those receiving sedative or analgesic medication or treatment for hypertension. Subjects were allocated randomly to receive either midazolam or ketamine by random number tables.

After an overnight fast, premedication comprised temazepam 20 mg orally, 1 h before the patient was studied. The study room was kept warm and quiet and patients were encouraged to relax as much as possible. During local anaesthesia, an i.v. cannula was inserted and a slow infusion of 0.9% saline was started through an infusion set fitted with an extension to allow drug administration without the knowledge of the patient.

Electrocardiograph electrodes were attached and the ECG displayed continuously. Non-invasive arterial pressure measurements were not obtained regularly because they could disturb the patient. The patient lay in the supine position with the head supported in a neutral position in the midline on a single soft pillow. The arms were supported at the sides and the recording apparatus was kept out of the line of vision of the patient.

EMG activity was recorded as in a previous study [6]. Briefly, the skin surface was prepared to obtain an inter-electrode resistance of < 2 kΩ. Disposable pre-gelled silver–silver chloride electrodes were placed with centres 3 cm apart, in the midline posterior to the lower edge of the mandible (tongue), just below the thyroid prominence (neck strap muscles) and over the right scalenus medius (scalene group), and recorded with the ECG using an FM

G. B. DRUMMOND, FRCA, University Department of Anaesthetics, Royal Infirmary, Edinburgh EH3 9YW. Accepted for publication: January 5, 1996.

Present address: Département d'Anesthésie et Réanimation, Hôpital Henri Mondor, 51 Ave du Mal. de Lattre de Tassigny, 94010 Créteil, France.

†Preliminary results of this study were presented to the Anaesthetic Research Society (*British Journal of Anaesthesia* 1989; 62: 230P).

tape recorder. In subsequent analyses the signals were rectified and integrated with a time constant of 100 ms after gating to remove the ECG component [12]. Recordings were made over at least 30 s. Maximum amplitude of the integral during the respiratory cycle was measured. The presence of phasic activity was classified as a variation in amplitude within the respiratory cycle of more than 50 % peak activity, during episodes when airway obstruction was judged to be minimal.

After attaching the electrodes, patients were encouraged to relax for at least 5 min without speaking before measurements were made of resting awake activity. Midazolam was given as an initial bolus of either 2 or 3 mg, according to age, and then in 1-mg or 0.5-mg doses at 3-min intervals to obtain a sedated state where the eyelids were drooping but not shut (the patient would respond either to a voice or light touch to the face) and the eyelash reflex was present.

Ketamine 1 mg kg^{-1} was given as a single dose. After administration the patients were not spoken to unless absolutely necessary, and given no specific instructions either to open or close the eyes. The ambient noise in the room was kept as small as practicable. Measurements were made 3 min after the last dose of midazolam, and at 2 and 4 min after administration of ketamine to provide some indication of the rate of onset of activity of this agent. In patients who received midazolam, further measurements were made during episodes of partial or complete airway obstruction and in some subjects, where possible, after relief of the obstruction by gentle support of the jaw or backward tilting of the head to obtain a clear airway with minimal arousal of the patient. The presence of airway obstruction was judged by clinical criteria, such as changes in gas flow felt at the mouth and nose, noise of breathing and pattern of chest and abdominal motion. In addition, in some patients changes in the movement of mouth and lips were noted. If the obstruction appeared severe, it was always remedied after 1 min. After measurements of muscle activity, administration of oxygen was started and anaesthesia was induced. After induction of anaesthesia and neuromuscular block, another recording of electrical activity was made to allow an exact measure of background electrical activity which was subtracted from the integral values.

Data were analysed using a spreadsheet (Excel v 5.0a) and a statistics package (Minitab release 8.2) using MS-DOS 6.2. Values are given as median (quartiles). Muscle activity, expressed as a percentage of the awake value, was converted to logarithms before statistical comparison; within subjects using the Wilcoxon test and between groups using the Mann–Whitney test. The incidence of phasic muscle activity was compared between groups with Fisher's exact test.

Results

The groups were comparable in age (53, 42–62 *vs* 64, 57–67 yr), height (178, 171–179 *vs* 175, 168–180 cm), weight (71, 63–75 *vs* 67, 61–83 kg) and weight as a percentage of expected weight (95, 90–108 % *vs* 103, 93–114 %) (respective values for midazolam and ketamine).

Table 1 Muscle activity (% of awake values) in the two groups, during periods when airway obstruction was judged to be minimal. Values are median (quartile) values

	Midazolam	Ketamine
Muscle group		
Tongue	42 (20–44)	72 (60–155)
Strap muscles of neck	28 (19–60)	175 (130–213)
Scalene muscle	33 (19–62)	100 (81–311)

The 12 patients who received midazolam were given a median dose of 5 mg (seven patients received 5 mg; dose range 3–8; quartiles 5 and 7 mg). In all patients the required end-points of sedation were reached and no patient was judged to have become oversedated. Airway obstruction occurred in 10 patients sedated with midazolam and patients were either repetitively aroused or the jaw was supported to restore airway patency. In another patient, breathing became noisy but there was no obstruction.

One patient received midazolam 8 mg, which was the largest dose required. If this patient is excluded, there was a significant decrease in dose requirements with age ($P < 0.05$), although the correlation was not strong ($r = 0.4$), indicating considerable variation in dose requirements, independent of age. The relationship between dose and age was less significant if the dose was considered in terms of actual or ideal body weight, although there was no relationship between body weight and age.

There was no difference in muscle activity at 2 and 4 min after administration of ketamine, and the 4-min measurements have been used for presentation and analysis. After ketamine, all patients became quiet and detached. None had clinically apparent airway obstruction.

Sedation with midazolam was associated with a significant reduction in muscle activity in all three muscle groups ($P < 0.01$), whereas there was no significant change in activity after ketamine (table 1).

Partial or complete airway obstruction developed in 10 of 12 patients who received midazolam. In all subjects there were changes in the sounds of airflow, and reductions in gas flow palpable at the airway opening. In six subjects there were changes in the pattern of movement of lips, cheeks, the suprahyoid region of the neck and the chest wall, particularly as the obstruction was prolonged. In patients who received midazolam, measurements during airway obstruction showed progressive increases in muscle activity that were more obvious in the strap muscles of the neck and the scalenes, although there were no significant differences in the increases in the three groups. A typical example is shown in figure 1 and the changes in all subjects are shown in figure 2. During episodes of airway obstruction, activity was phasic in two, six and seven subjects in the tongue, neck strap muscles and scalene muscles, respectively. When the obstruction was relieved, successful recording of activity was obtained in five subjects. In all of these subjects airway muscle activity decreased

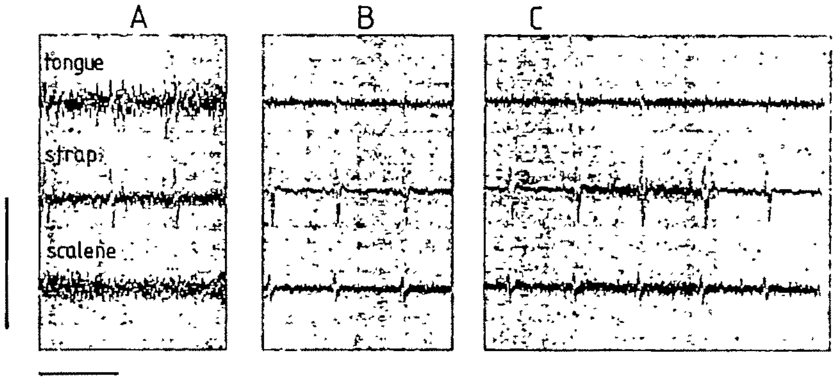


Figure 1 Representative recording of EMG signals in a patient who received midazolam. A = Awake; B = after sedation; and C = during an episode of partial airway obstruction. There is a marked reduction in tonic activity after sedation and an increase in phasic activation in time with inspiration during partial airway obstruction. (Vertical scale marker = 1 mV, horizontal scale marker = 1 s.)

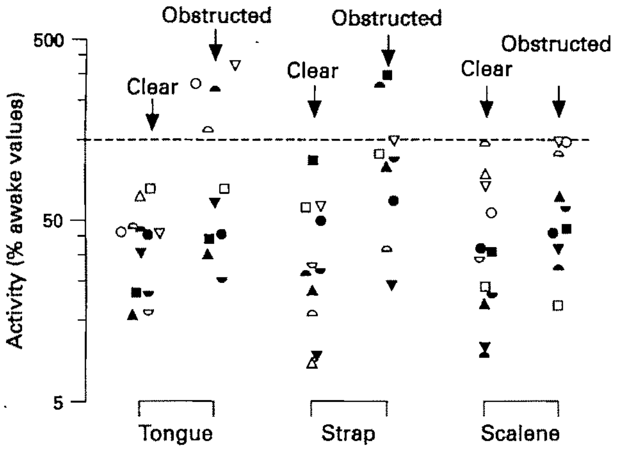


Figure 2 Changes in the activity of the three muscle groups (expressed as percentage of awake values) in patients sedated with midazolam, during episodes of clear breathing (all subjects) and obstructed breathing attempts (10 subjects). The dotted horizontal line indicates the awake activity. Each subject is shown by a different symbol. For subjects with airway obstruction, the increase in activity in each muscle group was significant ($P < 0.05$). Note that obstruction persisted despite activity in some patients being greater than the awake value.

considerably but there were insufficient numbers to allow statistical analysis of sufficient power by the Wilcoxon test.

There was evidence of phasic activity in five patients after ketamine sedation, but in only one subject was phasic activity seen in the tongue signal.

There were no adverse events in the study apart from episodes of airway obstruction, which were corrected promptly. No patient reported unpleasant experiences. The quality of recovery from the subsequent anaesthesia was not altered discernibly.

Discussion

Comparison of sedation with midazolam and ketamine is not simple. In clinical terms, the states of sedation were comparable. However, the ED_{95} for abolition of response to command by ketamine is approximately 0.6 mg kg^{-1} [13], and therefore the dose chosen in this study may have been larger than necessary. In contrast, the end-point of midazolam sedation was deliberately "light" and several patients became aroused by the manoeuvres used to restore airway patency. In patients who received midazolam it is also likely that there was considerable interaction between the drug effect and the sleep state. Such interactions may perhaps explain the discrepancies in previous results where airway obstruction was not observed after the use of similar or greater doses than in the present study [1, 4]. Another factor that complicates comparison between studies is the variation in susceptibility to midazolam with age [14]. The relative potencies of these two agents depend on the measure of effect that is used for comparison as they do not have parallel dose–response relationships [13]. The dose of midazolam relative to ketamine used in this study was less than the equivalent dose in a previous comparison [15], but the patients in that study were less healthy (ASA III or IV). In addition, in our study patients were premedicated with temazepam. This is likely to have had an additive influence on the effects of midazolam. For ketamine, which is a different class of agent, the effects are less easy to predict, but ketamine appears to have additive effects with propofol (which does act in a way similar to that of the benzodiazepines) [16]. Stella, Torri and Castiglioni [13] reported that the ED_{95} of ketamine for abolition of response to command was 0.6 mg kg^{-1} and for diazepam, which is generally considered to be approximately 50% as potent as midazolam, 0.5 mg kg^{-1}, which again suggests that the dose of midazolam used in this study was small in comparison with the dose of ketamine.

Additional measurement of airway or oesophageal pressure would have allowed more exact assessment of the relationship between muscle action, airway pressure and resistance changes. However, such measurements are more invasive and more likely to alter arousal and consequent responses than the presence of external electrodes. On the other hand, inductance band measurements of the rib cage and abdomen would have caused no disturbance to patients and might have confirmed previous observations of the pattern of rib cage movement during sedation with midazolam [17] which have now been recognized as associated with airway obstruction [11].

The pattern of activity in the muscles studied was similar to that found in a previous study [6], although tongue activity was less often phasic than activity recorded using intramuscular electrodes placed via the mouth [18, 19]. Previous workers have reported variations in the pattern of activity depending on the site of measurements [20]. In normal subjects, genioglossus activity is greater in the supine than the sitting position, and greater when breathing via the nose than the mouth [19]. These factors may have a bearing on the present results as from clinical experience and previous observations [6], increasing sedation alters the route of respiration from the nose to the mouth, probably with loss of muscle tone in the soft palate, and a change in the breathing route may contribute to loss of tongue muscle activity. Our observations of scalene muscle activity are also in agreement with previous reports [6, 21–23] but not with a more recent study using intramuscular electrodes [24] in which no activity was found during quiet respiration in the supine position.

In this study, administration of ketamine was not associated with loss of airway patency or with a decrease in airway muscle activity, consistent with previous animal studies [9]. Previous studies in humans with ketamine 1 mg kg^{-1} reported greater resistance to aspiration of radio-opaque markers than with other sedatives such as diazepam [25]. In contrast, there was marked loss of airway muscle activity and airway patency with administration of midazolam. Animal studies in particular indicate the relative importance of the neck muscles in the control of airway patency [26, 27].

Sedation with midazolam 0.1 mg kg^{-1} increases nasal airway resistance in supine subjects [8] and causes a reduction in inspiratory flow and snoring in male, or female, subjects with partial nasal obstruction [11]. The obstruction causes an increase in the relative contribution of the rib cage to respiratory movement [11, 17] which suggests reflex activation of rib cage muscles such as the scalenes, which can contribute to rib cage movement [28–31], and is consistent with our observations. Such abnormalities of movement in sedated patients can be reversed by application of positive airway pressure [32].

The progressive increase in activation of the muscles during obstruction has been noted in previous studies [18] but does not appear to be a universal finding in sleeping patients. The mechanism is unclear. Although there are reflexes associated with upper airway sensation [33–35], and in animals from lung volume feedback [36], there is also a progressive increase which resembles the probable increase in chemical drive. It is possible that arousal from the sedated state might have occurred if the airway muscle activity had been allowed to increase further, as occurs in sleep apnoea [37].

This study suggests that when male patients are sedated with midazolam, even if they remain easily rousable, close attention must be paid to their airway, and airway support is likely to be required. In contrast, ketamine sedation is not likely to reduce airway muscle activity and impair upper airway patency. The results of this study, together with previous studies [11, 17], also suggest that observation of movements of the rib cage may be misleading in the assessment of the presence of airway obstruction, as most observers probably associate breathing difficulty with reduced rib cage excursion.

Acknowledgement

This study was supported by a grant from the Biomedical Research Committee of the Scottish Home and Health Department for the purchase of measuring and recording equipment.

References

1. McClure JH, Brown DT, Wildsmith JAW. Comparison of the i.v. administration of midazolam and diazepam as sedation during spinal anaesthesia. *British Journal of Anaesthesia* 1983; 55: 1089–1093.
2. Al-Khudairi D, Whitwam JG, McClay RF. Midazolam and diazepam for gastroscopy. *Anaesthesia* 1982; 37: 1002–1006.
3. Smith DC, Crul JF. Oxygen desaturation following sedation for regional anaesthesia. *British Journal of Anaesthesia* 1989; 62: 206–209.
4. Manara AR, Smith DC, Nixon C. Sedation during spinal anaesthesia: a case for the routine administration of oxygen. *British Journal of Anaesthesia* 1989; 63: 343–345.
5. Caplan RA, Ward RJ, Posner K. Unexpected cardiac arrest during spinal anesthesia: a closed claims analysis of predisposing factors. *Anesthesiology* 1988; 68: 5–11.
6. Drummond GB. Influence of thiopentone on upper airway muscles. *British Journal of Anaesthesia* 1989; 63: 12–21.
7. Leiter JC, Knuth SL, Krol RC, Bartlett D. The effect of diazepam on genioglossal muscle activity in normal human subjects. *American Review of Respiratory Disease* 1985; 132: 216.
8. Montravers P, Dureuil B, Desmonts JM. Effects of i.v. midazolam on upper airway resistance. *British Journal of Anaesthesia* 1992; 68: 27–31.
9. Rothstein RJ, Narce SL, deBerry-Borowiecki B, Blanks RHI. Respiratory-related activity of upper airway muscles in anesthetized rabbit. *Journal of Applied Physiology* 1983; 55: 1830–1836.
10. Leiter JC, Doble EA, Knuth SL, Bartlett D. Respiratory activity of genioglossus. Interaction between alcohol and the menstrual cycle. *American Review of Respiratory Disease* 1987; 135: 383–386.
11. Masuda A, Haji A, Wakasugi M, Shibuya N, Shakunaga K, Ito Y. Differences in midazolam-induced breathing patterns in healthy volunteers. *Acta Anaesthesiologica Scandinavica* 1995; 39: 785–790.
12. Muller N, Volgyesi G, Becker L, Bryan MH, Bryan AC. Diaphragmatic muscle tone. *Journal of Applied Physiology* 1979; 47: 279–284.
13. Stella L, Torri G, Castiglioni CL. The relative potencies of thiopentone, ketamine, propanidid, alphaxalone and diazepam. *British Journal of Anaesthesia* 1979; 51: 119–122.
14. Bell GD, Spickett GP, Reeve PA, Morden A, Logan RFA. Intravenous midazolam for upper gastrointestinal endoscopy: a study of 800 consecutive cases relating dose to age and sex of patient. *British Journal of Clinical Pharmacology* 1987; 23: 241–243.
15. Gross JB, Caldwell CB, Edwards MW. Induction dose–response curves for midazolam and ketamine in premedicated ASA class III and IV patients. *Anesthesia and Analgesia* 1985; 64: 795–800.
16. Hui TW, Short TG, Hong W, Suen T, Gin T, Plummer J. Additive interactions between propofol and ketamine when used for anesthesia induction in female patients. *Anesthesiology* 1995; 82: 641–648.
17. Morel DR, Forster A, Bachmann M, Suter PM. Effect of intravenous midazolam on breathing pattern and chest wall mechanics in humans. *Journal of Applied Physiology* 1984; 57: 1104–1110.
18. Kuna ST, Smickley J. Response of genioglossus muscle activity to nasal airway occlusion in normal sleeping adults. *Journal of Applied Physiology* 1988; 64: 347–353.

19. Douglas NJ, Jan MA, Yildirim N, Warren PM, Drummond GB. Effect of posture and breathing route on genioglossal EMG activity in normal subjects and in patients with the sleep apnea/hypopnea syndrome. *American Review of Respiratory Disease* 1993; **148**: 1341–1345.
20. Sauerland EK, Harper RM. The human tongue during sleep: electromyographic activity of the genioglossus muscle. *Experimental Neurology* 1976; **51**: 160–170.
21. Druz WS, Sharp JT. Activity of respiratory muscles in upright and recumbent humans. *Journal of Applied Physiology* 1982; **51**: 1552–1561.
22. De Troyer A, Estenne M. Coordination between rib cage muscles and diaphragm during quiet breathing in humans. *Journal of Applied Physiology, Respiratory Environmental and Exercise Physiology* 1984; **57**: 899–906.
23. Drummond GB. Reduction of tonic ribcage muscle activity by anesthesia with thiopental. *Anesthesiology* 1987; **67**: 695–700.
24. Warner DO, Warner MA, Ritman EL. Human chest wall function while awake and during halothane anesthesia. I. Quiet breathing. *Anesthesiology* 1995; **82**: 6–19.
25. Carson IW, Moore J, Balmer JP, Dundee JW, McNabb TG. Laryngeal competence with ketamine and other drugs. *Anesthesiology* 1973; **38**: 128–133.
26. van Lunteren E, Haxhiu MA, Cherniack NS. Relationship between upper airway volume and hyoid muscle length. *Journal of Applied Physiology* 1987; **63**: 1443–1449.
27. van Lunteren E, Haxhiu MA, Cherniack NS. Mechanical function of hyoid muscles during spontaneous breathing in cats. *Journal of Applied Physiology* 1987; **62**: 582–590.
28. Raper AJ, Thompson WT, Shapiro W, Patterson JL. Scalene and sternomastoid muscle function. *Journal of Applied Physiology* 1966; **21**: 497–502.
29. Danon J, Druz WS, Goldberg NB, Sharp JT. Function of the isolated paced diaphragm and the cervical accessory muscles in C1 quadriplegics. *American Review of Respiratory Disease* 1979; **118**: 373–390.
30. Saumarez RC. An analysis of possible movements of human upper rib cage. *Journal of Applied Physiology* 1985; **60**: 678–689.
31. Saumarez RC. An analysis of action of intercostal muscles in human upper rib cage. *Journal of Applied Physiology* 1986; **60**: 690–701.
32. Nozaki-Taguchi N, Isono S, Nishino T, Numai T, Taguchi N. Upper airway obstruction during midazolam sedation: modification by nasal CPAP. *Canadian Journal of Anaesthesia* 1995; **42**: 685–690.
33. McBride B, Whitelaw WA. A physiological stimulus to upper airway receptors in humans. *Journal of Applied Physiology* 1981; **51**: 1189–1197.
34. McNicholas WT, Coffey M, McDonnell T, O'Regan R, Fitzgerald MX. Upper airway obstruction during sleep in normal subjects after selective topical oropharyngeal anesthesia. *American Review of Respiratory Disease* 1987; **135**: 1316–1319.
35. DeWeese EL, Sullivan TY. Effects of upper airway anesthesia on upper airway patency during sleep. *Journal of Applied Physiology* 1988; **64**: 1346–1353.
36. van Lunteren E, Strohl KP, Parker DM, Bruce EN, Van de Graaff WB, Cherniack NS. Phasic volume-related feedback on upper airway muscle activity. *Journal of Applied Physiology* 1984; **56**: 730–736.
37. Vincken W, Guilleminault C, Silvestri L, Cosio M, Grassino A. Inspiratory muscle activity as a trigger causing the airways to open in obstructive sleep apnea. *American Review of Respiratory Disease* 1987; **135**: 372–377.

British Journal of Anaesthesia 1996; **76**: 668–672

Accumulation of foreign gases during closed-system anaesthesia

L. VERSICHELEN, G. ROLLY AND H. VERMEULEN

Summary

In a previous study, accumulation of methane was found at the end of closed-system ventilation. As on-line analysis of gas concentrations is now available, we examined the progressive increase in concentrations of methane, carbon monoxide and acetone during modern, closed-system conditions, and their influence on infrared halothane analysis, in 26 non-pregnant, gynaecological patients. A computer-controlled closed-system anaesthesia apparatus (PhysioFlex) was used for ventilation during total i.v. anaesthesia (excluding nitrous oxide or potent inhalation anaesthetics) for gynaecological laparoscopy. Methane, carbon monoxide and acetone concentrations were analysed every 15 min in a photoacoustic infrared monitor and halothane concentrations by built-in infrared spectrometry. Mean methane concentrations increased progressively after 105 min to 941 (SD 1094) ppm, but concentrations of carbon monoxide and acetone did not increase significantly. In 18 patients, the infrared measurement falsely indicated 0.79 (0.52) % "halothane" after 60 min, but no reading appeared in the other eight patients. We conclude that methane accumulated progressively under strict closed-system conditions in higher concentrations than reported previously. In two-thirds of patients it induced false "halothane" readings. (*Br. J. Anaesth.* 1996; **76**: 668–672)

Key words

Equipment, breathing systems. Gases non-anaesthetic, methane. Gases non-anaesthetic, carbon monoxide. Gases non-anaesthetic, acetone. Measurement techniques, spectrometry.

Modern anaesthetic machines permit low-flow or even totally closed-system anaesthesia. It is known that foreign gases accumulate during closed-system anaesthesia, and that methane in particular can be detected in moderate concentrations [1]. Recently, however, we found that methane was present at the end of closed-system ventilation in much greater concentrations than expected [2].

In animals, during total i.v. anaesthesia, expired false "halothane" concentrations of up to 0.8% have been recorded during rebreathing [3]. As herbivores partly expel methane via the lungs [4], it might be that methane affects the infrared measurement of halothane. In human, we unexpectedly found that closed-system ventilation during i.v. anaesthesia was associated sometimes with falsely recorded "halothane" concentrations [2].

As methods for on-line analysis of gases have become available recently, we have examined the progressive increases in concentrations of methane, carbon monoxide and acetone under modern closed-system conditions, and also the influence of methane on infrared analysis of halothane.

Patients and methods

Since 1989, we have routinely used a computer-controlled anaesthetic apparatus, PhysioFlex (Physio, The Netherlands) in clinical practice. The apparatus has been described in detail previously [5]. In brief, it is a closed system with a volume of 3.5 litre, wherein small amounts of oxygen, nitrous oxide (or air) are given by built-in, computer-controlled injection; excess gases are evacuated if necessary (fig. 1). The inspiratory oxygen concentration is measured continuously with a paramagnetic oxygen analyser, whereas concentrations of nitrous oxide, carbon dioxide and volatile anaesthetics are measured with a built-in, non-agent-specific infrared spectrometer (Andros, Berkeley, CA, USA). Measurement of halothane, enflurane or isoflurane can be set at an infrared wavelength of 3.3 µm. If no particular anaesthetic agent is selected for measurement, halothane sensitivity is chosen automatically in the apparatus used by us. If so chosen, liquid anaesthetic is injected by a computer-controlled syringe. Four-membrane chambers are built into the breathing system for the purpose of controlled ventilation. The apparatus can be used for inhalation anaesthesia or for oxygen–air ventilation, as in this study.

Recently, apparatus became available for measuring trace concentrations of gases. Using the Brüel and Kjaer multi-gas monitor 1302 (Denmark), trace concentrations are determined by a photoacoustic infrared method. At chosen moments, samples of 140 ml of breathing gases can be obtained for analysis, which is performed with dedicated, narrow-band optical filters. In this study, concentrations of methane were measured at a wavelength of 3.6 µm, while carbon monoxide and acetone were analysed at 4.7 and 8.5 µm, respectively. To avoid interference

---

L. VERSICHELEN, MD, G. ROLLY, MD, PHD, H. VERMEULEN, MD, Department of Anaesthesia, University Hospital, De Pintelaan, 185, B-9000 Ghent, Belgium. Accepted for publication: September 20, 1995.

Correspondence to G.R.

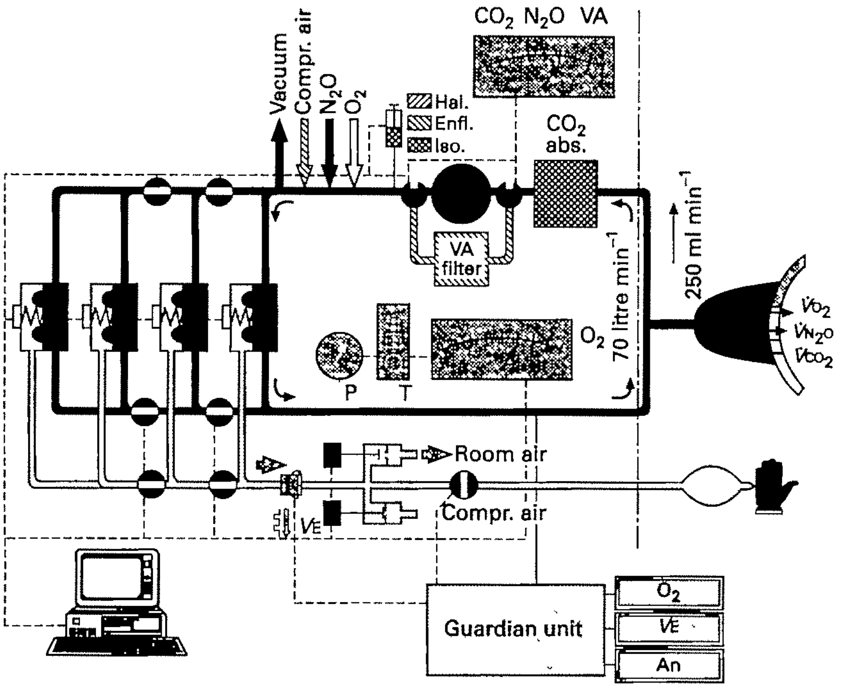


Figure 1 Direction of gases flowing at a flow rate of 70 litre min^{-1} in the circle is shown by the four arrows. No unidirectional valves are present. Inflow of oxygen (O_2), nitrous oxide (N_2O) or compressed air, and eventual injection of liquid halothane (Hal.), enflurane (Enfl.) or isoflurane (Iso.) is shown in the upper part. Excess gases are evacuated by vacuum. The four-membrane chambers are shown to the left. Windows showing carbon dioxide (CO_2), N_2O and volatile anaesthetics, and oxygen concentrations are shown. At the bottom, the Guardian unit is depicted.

at these specific wavelengths, the concomitant use of nitrous oxide and potent inhalation anaesthetics was avoided, and the PhysioFlex apparatus was flushed carefully with oxygen before each use to eliminate any trace of these agents.

After 5 min of closed-system use, and every 15 min thereafter, 140-ml samples of gas were obtained directly at the Y-piece of the breathing circuit via a polytetrafluoroethylene tube and fed into the measuring chamber of the multi-gas monitor, while controlled ventilation was maintained continuously with the PhysioFlex apparatus. Although only oxygen and air were used, and no inhalation anaesthetic was given or selected for measurement, the analyser for halothane is always operational and readings are shown at the appropriate window on the screen. This non-invasive assessment was approved by the Ethics Committee of the hospital.

Total i.v. anaesthesia (TIVA), with oxygen–air ventilation, is used routinely in our department for gynaecological laparoscopy with insufflation of carbon dioxide. TIVA is performed with propofol 1–2.5 mg kg^{-1}, followed by continuous administration at a rate of 10 mg kg^{-1} h^{-1}, and fentanyl (intermittent 0.1-mg boluses as required clinically). Vecuronium 0.1 mg kg^{-1} is used for intubation and surgical neuromuscular block. Controlled ventilation with an $F\text{I}_{O_2}$ of 0.4 is used, with minute volumes to maintain end-tidal $P\text{CO}_2$ at 4.0–4.6 kPa.

Statistical analysis of the data was done using the following tests: Mann–Whitney *U*-test, Wilcoxon signed rank test and Student's *t* test, where appropriate, for comparison of variables at different times within a group and at similar times between groups; ANOVA, Wilcoxon test and Friedman test, where appropriate, for detection of variation in time within a group; and two-way ANOVA for comparison between groups.

Results

We studied 26 ASA I or II, non-pregnant women undergoing routine gynaecological laparoscopy. Mean age, weight and height are shown in table 1, together with the occurrence of "false" halothane readings. Anaesthesia lasted 60–235 min.

A progressive increase in methane concentration was found with time ($P = 0.002$; ANOVA); concentrations of carbon monoxide did not change significantly with time (table 2). A reading for inhalation anaesthetic concentration was present in 18 patients; it did not appear, or occasionally gave the lowest reading possible on the screen, in eight patients. For analysis of the results, patients were therefore allocated to one of two groups according to the presence (group A) or absence (group B) of readings for inhalation anaesthetic values.

Concentrations of methane in the 18 patients in group A were significantly higher than in the eight

Table 1 Patient characteristics in relation to false "halothane" readings (mean (SD or range))

	Presence of "halothane" reading ($n = 18$)	Absence of "halothane" reading ($n = 8$)	Total group ($n = 26$)
Age (yr)	42.7 (29–78)	39.0 (28–77)	41.6 (28–78)
Weight (kg)	62.8 (11.4)	67.6 (10.3)	64.2 (11.0)
Height (cm)	165.1 (7.6)	167.0 (9.0)	165.7 (7.9)

Table 2 Mean (SD) concentrations of methane, carbon monoxide (CO) and acetone measured at progressive times in the total group of 26 patients (overall statistical difference with time was $P < 0.002$ for methane; ns for CO)

	5 min ($n = 26$)	15 min ($n = 26$)	30 min ($n = 26$)	45 min ($n = 26$)	60 min ($n = 26$)	75 min ($n = 20$)	90 min ($n = 13$)	105 min ($n = 11$)
Methane (ppm)	240 (211)	374 (253)	510 (398)	594 (513)	671 (582)	789 (746)	802 (971)	941 (1094)
CO (ppm)	26.0 (30.5)	21.9 (28.6)	20.7 (25.7)	20.4 (23.4)	20.4 (21.8)	21.0 (22.8)	23.7 (27.1)	25.8 (28.3)
Acetone (ppm)	31.6 (28.7)	35.8 (35.1)	38.7 (39.9)	38.9 (42.3)	39.4 (42.7)	56.6 (97.0)	69.4 (110.8)	40.2 (33.4)

Table 3 Methane and false "halothane" concentrations in group A ($n = 18$) and methane concentrations in group B ($n = 8$) (mean (SD)). Results up to 60 min only were available from every patient. *$P < 0.05$, **$P < 0.01$ *vs* 5 min; †$P < 0.05$, ††$P < 0.01$ *vs* 15 min; ‡‡$P < 0.01$ vs 30 min

	5 min	15 min	30 min	45 min	60 min
Group A					
Methane (ppm)	295 (233)	458 (249)*	664 (385)**	793 (499)**†	899 (564)**††
"Halothane" (%)	0.14 (0.07)	0.27 (0.19)**	0.46 (0.36)**	0.64 (0.44)**††	0.79 (0.52)**††‡‡
Group B					
Methane (ppm)	116 (52)	185 (140)	162 (74)	145 (52)	158 (22)

Table 4 Mean (SD) concentrations of acetone and carbon monoxide (CO) in groups A ($n = 18$) and B ($n = 8$); (no significant difference overall for acetone and CO, both with time and between groups)

	5 min	15 min	30 min	45 min	60 min
Group A					
Acetone (ppm)	36.8 (31.1)	39.7 (38.3)	42.5 (42.1)	41.6 (42.8)	41.5 (44.8)
CO (ppm)	30.1 (35.6)	25.5 (33.8)	23.8 (30.5)	23.4 (27.7)	23.3 (25.8)
Group B					
Acetone (ppm)	20.0 (19.5)	27.1 (26.5)	30.1 (35.2)	32.9 (43.3)	34.7 (40.0)
CO (ppm)	16.9 (9.9)	13.7 (6.1)	13.8 (5.0)	13.5 (3.9)	13.9 (3.5)

patients in group B (table 3). In group A, a progressive increase in methane concentration was noticed ($P < 0.05$ or $P < 0.01$; Wilcoxon signed rank and Friedman's test), as was an increase in the reading for inhalation anaesthetic ($P < 0.01$; Wilcoxon signed rank and Friedman's test). A significant ($P < 0.015$) correlation was found between methane (X) and the anaesthetic reading (Y): "halothane" $\% = (8.5 \times \text{methane (ppm)} \times 10^{-4}) - 0.069$ ($r^2 = 86.10\%$). In group B, there was no statistically significant difference in methane concentration at different times.

Mean values for both carbon monoxide and acetone were higher in group A than group B (table 4). Although no significant changes with time were found for carbon monoxide, concentrations of acetone increased marginally with time.

Discussion

Methane is present in the alimentary tract of animals and humans. It is produced primarily in the distal colon by fermentation of carbohydrates under strict anaerobic conditions by *Methanobacterium ruminatium*. Methane is liberated by reduction of carbon dioxide with hydrogen [6]. Intestinal gas in humans contains up to 26% methane [7]. The main part is excreted in flatus, but a smaller part is taken up in blood. Because of the insolubility of methane in blood relative to air, 90–95% of this gas is cleared in a single passage through the lungs. There are large individual differences: approximately two-thirds of subjects had methane breath concentrations of less than 1 ppm, and one-third concentrations ranging from 1 to 70 ppm [8]; 80% of patients with cancer of the large bowel had detectable levels of methane in their breath [9] and 83% of patients with aorto-iliac disease [10]. Also, patients with extensive ulcerative colitis and colonic polyposis produce high concentrations of methane [11].

Using modern, true closed-system conditions, we have shown that methane not only accumulated in concentrations 10 times higher than reported previously [1], but that the extent of the accumulation was also highly individual. Indeed, two-thirds of our patients had high initial values that increased further with time, whereas one-third had lower values that only moderately and non-significantly increased with time. In one patient a concentration of 4130 ppm was noted, which is more than 15 times the maximum value of 229 ppm found after 72 min by Morita, Latta and Snider [1].

An interesting aspect is that, in our sample of patients, two-thirds were high methane exhalers, whereas in the apparently normal population, two-thirds had only traces of methane excretion [8]. Our patients were women, undergoing laparoscopy for gynaecological reasons. None had ulcerative colitis, aorto-iliac disease or cancer of the large bowel. Even the "low" methane exhalers had pronounced concentrations of gas under closed-system conditions. We cannot explain this but we speculate that laparoscopic pneumoperitoneum induced with carbon dioxide might be a contributing factor. Unfortunately, for technical and practical reasons, baseline measurements of pre-anaesthetic methane excretion could not be made in most of our patients. Allocation of our patients to two groups was made solely on the presence or absence of false "halothane" readings on the PhysioFlex apparatus. Retrospective analysis of the findings for methane shows that, on average, values greater than 150–175 ppm influenced the infrared measurement. However, in three patients, even lower values induced "halothane" readings, whereas in four patients, values up to 389 ppm did not consistently activate the infrared sensor. We therefore speculate that methane was not the only factor disturbing the measurement of inhalation concentration. It has been suggested previously that other hydrocarbons such as acetone might interfere with this [3]. Nevertheless, in our "high" methane exhalers, there was a positive correlation between methane concentration and the false "halothane" concentration on the screen. The highest recorded value was 3.7%, coinciding with a methane concentration of 4130 ppm.

Acetone produced in the liver during metabolism of free fatty acids is excreted partly by the lungs [12]; during fasting there is increased pulmonary excretion [12]. In our study acetone concentrations were, on average, double those found by Morita, Latta and Snider [1], and tended to increase with time, although this was not significant. It has been reported that flushing the system with fresh gas fails to decrease the acetone concentration [1]; this aspect was not analysed here.

Carbon monoxide in alveolar air may be exogenous or endogenous. Cigarette smoke and accidental inhalation of carbon monoxide are examples of the first, whereas endogenously formed carbon monoxide is a by-product of haemoglobin catabolism. Accumulation of carbon monoxide during closed-system anaesthesia was studied as long ago as 1965; values of 0–210 ppm were reported [13], and two-thirds of patients showed an increase in carbon monoxide concentration with time, whereas one-third had no increase or a decrease. In another report, it was stated that concentrations of carbon monoxide decreased in similar circumstances [14]. In this study, values of carbon monoxide of 7.5–164 ppm were found. This last, single, extremely high value influenced greatly the mean in the first group (A). There was no statistically significant difference in carbon monoxide concentrations either between the two groups (A and B) or with time. In three patients an increase and in eight a decrease was seen with closed-system anaesthesia, whereas in 15 patients there was no pronounced change.

The clinical implications of progressively increasing concentrations of methane and acetone are not clear. It has been suggested that with concomitant intake of alcohol, they could reach flammable levels [1]. However, personnel in submarines are often exposed to methane and acetone for months without adverse effects. The concentration limits of the US Navy for acetone and methane for 24 h are 2000 and 5000 ppm, respectively, and it has been argued that concerns about these trace contaminants are unfounded [15]. Although concentrations of acetone measured here were lower than those accepted as toxic, in one patient concentrations of methane were close to toxic levels. However, we never flushed the system deliberately, except before use, and therefore methane concentrations were increased by the chosen method. In normal practice it is customary to flush the system at least every 2 h [14]. Concentrations of methane should be significantly lower during everyday clinical practice with closed-system anaesthesia.

The erroneous influence on the infrared measurement set at 3.3 µm, as used in most inhalation anaesthetic monitors, is disturbing. Our results showed an impressive effect, with a linear relation between methane and the falsely recorded "halothane" concentration. Blindly following the monitored halothane concentration during closed-system or minimal-flow anaesthesia would be hazardous. The false halothane concentration incites lowering of the vaporizer output, with the inherent danger of too light anaesthesia and the possibility of awareness. In the PhysioFlex apparatus, automatic injection of liquid anaesthetic is computer-controlled in a closed loop according to the measured infrared concentrations. Some years ago the use of a feedback loop for halothane was already being questioned, as too low halothane values were recorded by mass spectrometry [16].

Techniques in which potent inhalation anaesthetics are analysed at higher infrared wavelengths (10–13 µm) are not influenced by the presence of methane. These should be preferred during closed-system anaesthesia, or alternatively other techniques, such as mass spectrometry or Raman scattering. Recently, for the PhysioFlex apparatus, an alternative, second method for measuring inhalation anaesthetics (Guardian Unit: piëzo-electrical sensor) has also been built in, the difference between measurements on the two devices providing evidence for the presence of foreign gases such as methane. In the most recent version of the PhysioFlex apparatus, the infrared readout is switched off automatically when no potent inhalation anaesthetic has been selected and used.

References

1. Morita S, Latta W, Snider M. Accumulation of methane, acetone and nitrogen in the inspired gas during closed-circuit anesthesia. *Anesthesia and Analgesia* 1985; **64**: 343–347.
2. Rolly G, Versichelen L, Mortier E. Methane accumulation during closed circuit anesthesia. *Anesthesia and Analgesia* 1994; **79**: 545–547.
3. Taylor PM. Interference with the Datex Normac anaesthetic agent monitor for halothane in horses and sheep. *Journal of the Association of Veterinary Anaesthesia* 1990; **17**: 32–34.
4. Christensen K, Thorbek G. Methane excretion in the growing pig. *British Journal of Nutrition* 1987, **57**: 355–361.
5. Rendell-Baker L. Future directions in anesthesia apparatus. In: Ehrenwerth J, Eisenkraft JB, eds. *Anesthesia Equipment—Principles and Applications*. Chicago: Mosby-Yearbook Inc, 1993; 691–694.
6. Stadtman TC. Methane fermentation. *Annual Review of Microbiology* 1967; **21**: 121–142.
7. Levitt MD, Bond JH. Volume, composition and source of intestinal gas. *Gastroenterology* 1970; **59**: 921–929.
8. Bond JH, Engel RR, Levitt MD. Factors influencing pulmonary methane excretion in man. *Journal of Experimental Medicine* 1971; **133**: 572–588.

9. Haines A, Metz G, Dilawari J, Blendis L, Wiggins H. Breath methane in patients with cancer of the large bowel. *Lancet* 1977; **ii**: 481–483.
10. McKay LF, Brydon WG, Eastwood MA, Honsley E. The influence of peripheral vascular disease on methanogesis in man. *Atherosclerosis* 1983; **47**: 77–81.
11. Piqué JM, Pallares M, Cuso E, Vilar-Bonet J, Gassull MA. Methane production and colon cancer. *Gastroenterology* 1984; **87**: 601–605.
12. Crofford OB, Mallard RE, Winton RE, Rogers NL, Jackson JC, Keller U. Acetone in breath and blood. *Transactions of the American Clinical and Climatological Association* 1977; **88**: 128–139.
13. Middleton V, Van Poznak, A, Artusio JF, Smith SM. Carbon monoxide accumulation in closed circle anesthesia systems. *Anesthesiology* 1965; **26**: 715–719.
14. Lowe HJ, Ernst EA. *The Quantitative Practice of Anesthesia—Use of Closed Circuit.* Baltimore/London: Williams and Wilkins, 1981; 13.
15. Baumgarten RK, Reynolds WJ. Much ado about nothing: Trace gaseous metabolites in the closed circuit. *Anesthesia and Analgesia* 1985; **64**: 1029–1030.
16. Rolly G, Versichelen L, Verkaaik A, Erdmann W, Soens E. Mass spectrometric analysis of a new closed-circuit anaesthesia apparatus (PhysioFlex^{R}). *European Journal of Anaesthesia* 1990; **7**: 333–334.

British Journal of Anaesthesia 1996; **76**: 673–679

A new tracheal tube for difficult intubation

M. R. J. WEST, M. M. JONAS, A. P. ADAMS AND F. CARLI

Summary

We have compared a new Portex tracheal tube with the Oxford tube in performing simulated grade 3 difficult intubations. The Portex tube was modified so that the bevel faced backwards, as in the Oxford tube. A gum elastic introducer was used with both tubes. The time taken and number of attempts needed were recorded, with changes in arterial pressure, heart rate and incidence of sore throat. Both tubes were successful in avoiding the problem of obstruction at the cords, which occurs when a standard Magill tube is used with an introducer. Thus the new tube has the merits of the Oxford tube without the disadvantages of rubber. It is suitable for both easy and difficult intubations with advantages in safety, cost and convenience. An unexpected but important finding was a clear learning effect, despite both investigators being familiar with the technique at the outset. Over the course of the study, intubation time decreased progressively ($P < 0.001$). This provides new evidence of the need for trainees to practise the art of intubation when the cords are not visible. Our estimate of the learning "half-life" was 15 intubations; we conclude that 30 simulated grade 3 intubations would be a reasonable objective for trainees before handling high-risk cases. (*Br. J. Anaesth.* 1996; **76**: 673–679)

Key words

Intubation tracheal. Intubation tracheal, complications. Intubation tracheal, training. Anaesthetist, training. Equipment, tubes tracheal.

Difficult intubation remains a key problem [1] and the value of a flexible introducer (gum elastic or wire) as a first approach is well recognized in the UK and USA [2]. It is the simplest method, effective for all grade 2 laryngoscopies, where at least the arytenoids are visible and most grade 3 laryngoscopies, where the epiglottis can be seen but no part of the glottis. Macintosh initiated the method [3] and also devised the Oxford tube [4] for use with an introducer. When a Magill tube is used with an introducer, it commonly becomes impacted at the cords, but the Oxford tube avoids this problem. However, it is made of rubber which is a disadvantage. This prompted us to see if a plastic version would be as effective as the original.

The Oxford tube also has a feature intended to minimize kinking, that is a reinforced bend, the effectiveness of which was confirmed in 18000 patients [5]. Our study was designed to compare the Oxford tube with a new plastic tube, primarily in relation to these two problems, snagging at the cords and kinking [6].

Patients and methods

The study took place at two hospitals, Guy's and Northwick Park. After obtaining Ethics Committee approval and informed consent, we studied 96 patients. Intubations were carried out by one trainee at each centre (M.M.J. and M.R.J.W.), each of whom had about 2 yr experience of anaesthesia and was familiar with the handling of bougies and the technique of simulated difficult intubation.

Misleading results could occur if, for example, one group had a larger number of edentulous patients, as it would appear to perform better even if the two tubes had identical properties. To avoid this error, patients were selected in pairs, matched roughly for ease of intubation. In practice this implied excluding patients with known stigmata of difficulty. Most were easy cases, converted to difficult intubations by a standard procedure. The pairs were healthy adults, allocated randomly to have a Portex or an Oxford tube. The study could not be performed blind, so the possibility of observer bias was kept in mind; the observers endeavoured to report not what was expected, but what happened. In the measurements recorded there is minimal scope for observer bias.

THE NEW TUBE

Portex Ltd agreed to manufacture a batch of tubes to our specifications. A standard tube was modified so that the bevel faced backwards, as in the Oxford tube. In all other respects it was identical to the widely used Portex Magill cuffed orotracheal tube

---

M. R. J. WEST*, MB, BS, FRCA, M. M. JONAS†, MB, BS, FRCA, A. P. ADAMS‡, MB, BS, PHD, FRCA, FANZCA, F. CARLI§ DMS, PHIL, FRCA, Department of Anaesthetics, United Medical and Dental School of Guy's and St Thomas's Hospitals, Guy's Hospital, London SE1 9RT and Division of Anaesthesia, Northwick Park Hospital, Harrow, HA1 3UJ. Accepted for publication: January 12, 1996.

Present addresses:

*Division of Anaesthesia, Derriford Hospital, Derriford Road, Plymouth PL6 8DH.

†Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford OX3 9DU.

§Department of Anaesthesia, McGill University, Royal Victoria Hospital, Montreal, Canada H3A 1A1.

‡Address for correspondence: Department of Anaesthetics, 2nd floor NGH, Guy's Hospital, London SE1 9RT.

(product number 100/166). The plastic has kink-resistant properties, so a reinforced bend was not considered necessary. Resistance to kinking is easily demonstrable *in vitro*, but needed confirmation *in vivo*. The introducer was a standard Eschmann gum elastic bougie (size 15 Ch (5 mm od)) and the laryngoscope was a size 3 Macintosh UK pattern (Penlon Ltd, Abingdon, Oxon, UK).

Premedication comprised lorazepam 2 mg i.m. for females and 3 mg i.m. for males. Anaesthesia was induced with thiopentone 3–4 mg kg^{-1} and maintained with 1–2 % enflurane and 70 % nitrous oxide in oxygen. Neuromuscular block was achieved with atracurium 0.5 mg kg^{-1}.

INTUBATION PROCEDURE

The key feature of a simulated difficult intubation [7] is to intubate while the vocal cords are not visible. Patients' lungs were ventilated for about 3 min with 2.5 % enflurane and 66 % nitrous oxide in oxygen. Laryngoscopy was carried out to expose the glottis, and the blade was deliberately lowered until the epiglottis obscured the cords. Size 8 (females) and size 9 (males) were used, with the introducer projecting 6–8 cm from the tube. Macintosh [4] pointed out that one of the advantages of the introducer is that it prevents the tube blocking the view at the critical moment; it must project far enough for this purpose. The introducer was directed immediately behind the epiglottis, in the mid-line, and advanced together with the tube. The introducer was then removed and the position of the tube verified clinically and by capnography. If the tube was in the oesophagus it was removed and the procedure repeated up to a maximum of three attempts.

Cricoid pressure was applied throughout to provide some indication of how the tubes would perform in emergency cases. The two-handed manoeuvre was used, the assistant placing one hand behind the neck to counteract displacement caused by his other hand. After successful intubation, a record was made of the number of attempts and intubation time, the time lapse between receiving the tube and verifying intubation. Arterial pressure was recorded before and 1 min after intubation.

TEST FOR OBSTRUCTION TO AIRFLOW

Airflow may be blocked by kinking or by the end of the tube becoming opposed to the tracheal wall. Both events cause an increase in airway pressure and both are most likely to occur on flexing the neck. After allowing 10 min for the tube to warm up towards body temperature, the neck was flexed gently to its maximum and the change in airway pressure recorded, using an aneroid manometer.

INCIDENCE OF POSTOPERATIVE SORE THROAT

After surgery, the patient was interviewed. If no complaint was volunteered a specific question was asked about sore throat.

SIGNIFICANCE TESTING

Routine *t* tests were applied to arterial pressure measurements, which were Gaussian; airway pressure was skewed, so Wilcoxon's rank sum test was used. Intubation times were also skewed (fig. 1), but after log transformation, they did not differ significantly from a normal distribution; the one-sample *t* test was used for paired data (comparing tubes) and the two-sample *t* test for unpaired data (comparing observers), both on logged data. Routine linear regression analysis was used to test if the progressive decrease in intubation time resulted from chance.

CURVE-FITTING—UNDERLYING EQUATION

The next step was to fit a more realistic model to the data. Common sense suggests that the true relation cannot be a straight line because that implies that intubation time decreases to zero. Moreover, learning is known to be a non-linear process in which the rate of improvement diminishes steadily, becoming zero when peak performance is reached. Scope for improvement is maximal at the start and zero at the end. If the rate of change is proportional to scope for change, an exponential curve results for reasons clearly explained by Nunn [8]. Learning involves several processes so the true relation is likely to be not a single exponential, but the sum of several.

However, the components of such a process cannot be disentangled realistically when the random error is large. We concluded that the most useful model would be a single exponential decline, such as occurs with radioactive decay. This is a reasonable compromise between the absurdity of a straight line and the ambiguity of a multi-exponential model. The equation of a simple exponential "die-away" curve is:

$$y = y_0 e^{-kn} + y_\infty$$

where y = dependent variable (intubation time) and n = independent variable (serial number of the intubation). There are four constants, the universal constant, e, and three others: y_∞ = "expert time", the time taken by the fully trained anaesthetist, the asymptote (i.e. if $n = \infty$ then $y = y_\infty$); y_0 = additional time required when there is no previous experience, so the "novice time" is $y_0 + y_\infty$ (i.e. if $n = 0$ then $y = y_0 + y_\infty$); k = learning constant, which measures the steepness of the curve, high values of k indicate quick learning $n - p$. (To simply descriptions of radioactivity, physicists have developed the concept of "half-life"; it may help to use the same idea here.)

The "half-life" can be thought of as the number of intubations needed to halve the distance between the novice time and the expert time. It is exactly predictable from k, using this equation:

$$\text{Half-life} = \frac{-\log_e(\frac{1}{2})}{k} = \frac{0.693}{k}$$

If the half-life is 15 then after 15, 30 and 45 intubations the amount of learning still to be done is 1/2, 1/4, 1/8, and so on. Serial numbering starts from 0, not 1, because most descriptions of exponential equations have the independent variable as time, starting at zero time. Thus allowing $n = 0$ for the first intubation leads to an equation identical to the one most commonly used and provides the useful results shown above in parentheses. y_0 can then be thought of as the extra time required when $n = 0$, that is previous experience is zero. Strictly our estimate of y_0 is that for a small n, not for $n = 0$, but that does not affect the other estimates, notably half-life.

CURVE-FITTING—LEAST SQUARES ESTIMATE

In principle the method is exactly the same as familiar linear regression. Gauss argued that the most likely values for slope and intercept are those which produce the smallest average deviation from the line, an idea which certainly appeals to common sense, if the deviations are symmetric. In practice the mathematics is simpler if we minimize not the mean deviation, but the mean squared deviation.

With non-linear processes the position is more complex because the direct route leads to an insoluble equation; that problem is surmounted by starting not from the basic equation, but from a first-order Taylor expansion of it [9]. From then on the route is essentially as mapped out by Gauss for linear regression. The same derivation works for any non-linear equation that can be differentiated. Computers reduce the labour of calculation greatly and make it easy to verify that the results are genuinely "least square". If any of the three constants is altered, up or down, and the variance recalculated, then it is always found to have increased, not a mathematical proof, but an easy and reassuring test.

CONFIDENCE LIMITS OF THE LEARNING CURVE

For linear regression the confidence limits of the slope are found by assuming that, in repeated sampling, the slopes follow a normal distribution and the same approach has been advocated for non-linear functions [10]. Computer simulations enable us to test this, as discussed elsewhere [11]. A program to simulate our study first uses the best fit values of y_0, y_∞ and k, found already, to produce a "perfect" set of y values with no scatter. Next a random number generator superimposes a scatter such that the y values acquire the same residual SD as the clinical observations. Each cycle of the program then yields results similar to the real data, on which a least squares analysis is carried out. The distribution of the variables was found to be highly skewed, particularly k; this invalidates the conventional route to the confidence limits. The modern computer displays the problem very clearly; it can also solve it. The main point of clinical importance is the lower 90% confidence limit of the half-life. To find this we must establish what half-life in the simulation produces exactly 5% of values as large as, or larger than, the best fit value for the real data. This is found by trial and error; after two "bracketing" shots the third estimate, by linear interpolation, is close to the required value, because over narrow ranges the relation is nearly linear.

Results

Patient co-operation was excellent; none declined. Both observers carried out 24 intubations with each tube, giving a total of 96 intubations for analysis (tables 1 and 2).

SUCCESS RATE

Sixty-two of the 96 intubations succeeded the first time, the others at the second or third attempts; the pre-set limit of three failures was never reached. For both tubes, entry to the larynx was smooth with no snagging at the cords. The number of cases in which intubation failed initially was not appreciably different for the two tubes (Oxford 16 of 48, Portex 18 of 48) (ns).

TESTS FOR OBSTRUCTION TO AIRFLOW

For observer 1, neck flexion caused changes in airway pressure with median 0 (range 0–6). For observer 2, the corresponding values were 0 (0–5). P was close to 1 in both.

CHANGES IN ARTERIAL PRESSURE

The mean change in arterial pressure 1 min after intubation was +14% (Oxford) and +12% (Portex) for observer 1 (ns); for observer 2 the values were +14% and +16% (ns). Other studies on routine intubation have shown that the pressor effect is maximal after 1 min and is usually approximately 27%. Thus the simulated difficult intubation drill caused no undue cardiovascular disturbance.

SORE THROAT

The incidence of sore throat was the same for both tubes (33%), which is close to the 34% reported for a similar study [12]. This compares favourably with 56% for routine intubation [13]. Our procedure did not appear to increase the likelihood of sore throat.

INTUBATION TIMES

Oxford tube vs *Portex tube* (n = *24*)

For observer 1, median intubation time was slightly longer for the Oxford tube (27.5 *vs* 21.5 s), while for observer 2 the opposite was true (20 *vs* 25 s). In neither case was the difference significant.

Observer 1 vs *observer 2* (n = *48*)

The (Oxford–Portex) differences did not differ significantly for the two observers and therefore the data were pooled. After pooling, the mean difference between the tubes was 1.3 s (ns), typical of cases

Table 1 Data of observer 1. Column 1 (C1) = serial number of intubation; C2 = intubation time (s); C3 = number of failures; C4 = change in arterial pressure 1 min after intubation; C5 = increase in airway pressure on flexing neck; C6 = postoperative sore throat

Oxford tube						Portex tube					
C1	C2	C3	C4	C5	C6	C1	C2	C3	C4	C5	C6
0	20	0	26	5	0	1	36	0	7	0	0
3	38	1	10	0	0	2	50	1	10	0	0
5	20	0	10	0	0	4	50	2	1	0	+
7	25	0	−5	0	+	6	28	0	−2	0	+
9	65	2	10	2	+	8	18	0	4	2	0
10	90	2	17	0	+	11	45	1	8	0	0
12	128	2	14	0	+	13	7	0	−12	0	0
14	35	1	10	5	0	15	6	0	10	0	+
17	7	0	−10	0	0	16	55	2	8	0	0
18	48	2	10	0	0	19	5	0	7	0	0
20	40	1	15	0	+	21	25	1	5	1	0
22	7	0	36	4	0	23	5	0	37	6	+
24	25	1	20	0	0	25	90	2	16	0	0
26	40	0	19	0	0	27	5	0	21	0	0
29	15	0	40	2	0	28	5	0	−10	2	0
31	40	1	5	0	+	30	10	0	20	0	0
33	40	1	21	0	+	32	29	1	−10	0	++
35	14	0	4	0	0	34	5	0	35	0	0
36	8	0	17	0	+	37	35	1	20	2	0
38	30	1	4	3	0	39	25	1	12	0	+
41	30	1	5	2	0	40	5	0	18	0	0
43	5	0	5	0	0	42	10	0	20	0	0
45	6	0	15	2	0	44	8	0	10	0	0
46	5	0	22	2	+	47	35	1	23	0	+

Table 2 Data of observer 2. Column 1 (C1) = serial number of intubation; C2 = intubation time (s); C3 = number of failures; C4 = change in arterial pressure 1 min after intubation; C5 = increase in airway pressure on flexing the neck; C6 = postoperative sore throat

Oxford tube						Portex tube					
C1	C2	C3	C4	C5	C6	C1	C2	C3	C4	C5	C6
0	29	0	6	0	0	1	20	0	14	0	0
3	35	0	−4	0	0	2	35	1	19	4	+
5	20	0	5	0	0	4	60	2	27	0	+
7	30	0	31	0	0	6	25	0	5	0	0
8	20	0	8	2	0	9	25	0	0	2	0
10	65	1	18	0	+	11	110	1	18	0	++
13	40	0	7	1	+	12	40	1	12	0	0
15	18	0	−2	0	+	14	18	0	10	3	0
17	20	0	13	0	0	16	25	0	22	0	+
18	15	0	17	0	0	19	65	1	21	0	+
20	25	0	6	0	+	21	25	0	15	0	0
22	12	0	9	0	0	23	25	0	16	0	0
24	35	1	36	0	0	25	18	0	21	0	0
27	14	0	12	0	+	26	16	0	15	1	0
29	50	1	19	4	+	28	21	0	10	2	0
31	22	0	6	0	0	30	14	0	−10	0	0
32	17	0	26	0	0	33	40	1	19	0	+
34	8	0	12	6	0	35	26	0	25	0	0
37	20	0	14	0	0	36	20	0	7	1	+
39	65	2	29	0	+	38	18	0	23	0	+
41	14	0	28	0	0	40	45	1	32	0	0
42	17	0	12	3	0	43	22	0	14	0	0
44	16	0	5	4	0	45	14	0	17	0	0
46	12	0	−2	0	0	47	42	1	6	0	+

where performance was essentially the same. However, a real difference might have been obscured by the scatter. Routine power analysis shows that if there were a real difference of 11.9 s and our study was repeated many times, then P would be less than 0.05 in 80 % of cases. A more rigorous test for, say, a difference of 2 s would need a very large sample. Proving a negative is notoriously difficult when the scatter is large and may not justify the cost.

As neither tubes nor observers differed significantly, all data were pooled ($n = 96$) (fig. 1). Median and interquartile range was 25 (14–40) s.

LEARNING EFFECT

The intubation times showed two distinct populations of data, a larger group in which intubation succeeded the first time and a smaller group with one

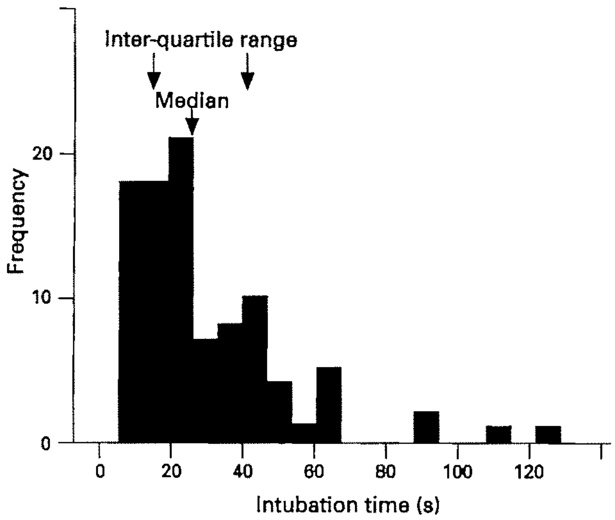


Figure 1 Histogram of intubation times for all 96 intubations carried out. Pooled data for both tubes and both observers.

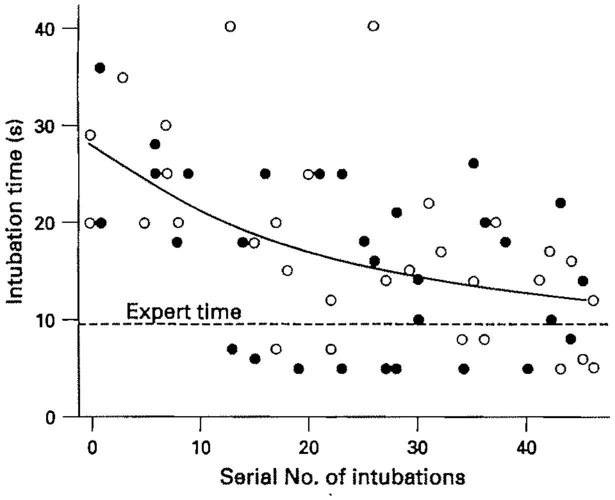


Figure 2 Intubation time *vs* serial number of the intubation for the 62 cases in which intubation was successful at the first attempt. ○ = Oxford tube, ● = Portex tube. (Note the similar performance by the two tubes and the progressive reduction in intubation time over the course of the study. The curve of best fit and its asymptote (expert time) was found by the method of least squares. It is an exponential curve with a half-life of 15 intubations.)

or two failures. Both showed evidence of a learning effect, but it was more clear-cut in the larger group, in particular, the residuals in this group were Gaussian (W' test, $P = 0.07$), as required for least squares analysis [14]. The next section deals with the larger group. Plotting intubation time against serial number of the intubation produced negative slopes for both tubes and both observers (differences between slopes were not significant) and therefore the four data sets were pooled. For the pooled data, the slope was significantly different from zero ($P = 4 \times 10^{-5}$); figure 6 in our abstract [6] shows the line of best fit and its 95% confidence limits. Next a learning curve was fitted. The least square values were : $y_0 = 18$ s, $y_\infty = 9.9$ s, $k = 0.046$, half-life = 15 s. Figure 2 shows the curve of best fit from these values.

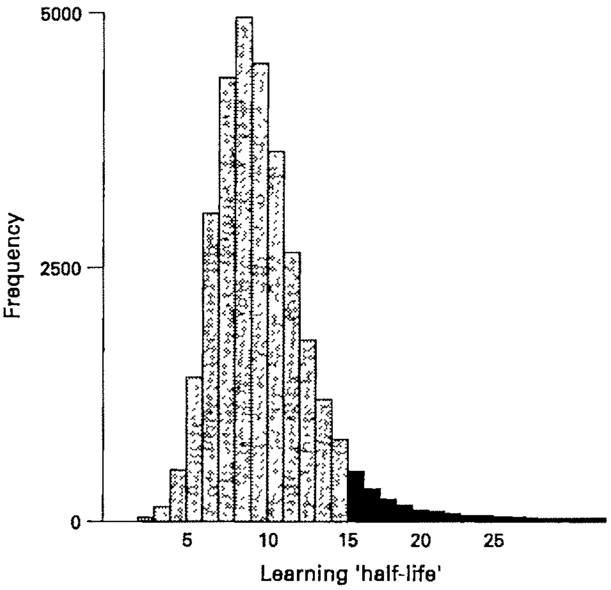


Figure 3 Lower confidence limit of the learning half-life, found by experiment. Computer simulations show what would happen if our study were repeated 30000 times. The variance of the simulated data matched that of the real data, but the half-life was adjusted not to 15, as in the real data, but to 9. The median value in the simulations was 9, but in 5% of cases a value of 15 or more was obtained (the black blocks). It follows that when the best fit value for the real data is 15, its lower 90% confidence limit is 9. This is a confidence limit by counting, as it were, not by calculation. Textbook calculation, assuming a symmetric distribution would clearly give the wrong answer.

LOWER 90% CONFIDENCE LIMIT OF THE LEARNING HALF-LIFE

The conventional lower 90% confidence limit (10.34) provided a first estimate. After entering this value in 30000 simulations, 5% of half-lives (HL) were more than 16.83, which is too high, so a lower value was entered in the next experiment

	HL entered	*Start of upper tail*	*Verdict*
Experiment 1	10.34	16.9	Too high
Experiment 2	8.66	14.6	Too low
Experiment 3	9.12	15.1	Correct

The third experiment gives the required value of 15 (fig. 3)

One advantage of creating an artificial population is that the "true" values, stripped of random variation, are known. In the experiments above, mean and mode differed widely from the true value, but the median agreed extremely well:

	True value	*Median*	*Mean*	*Mode*
Experiment 1	10.34	10.33	10.84	9.84
Experiment 2	8.66	8.67	9.14	8.21
Experiment 3	9.12	9.11	9.58	8.47

The mean is about 5% too high, the mode about 5% too low, but the median has no appreciable error. This supports the view that in a highly skewed population the best estimate of the focal point, as it were, is the not the mean, but the median. Of course for Gaussian populations, mean, mode and median coincide.

Discussion

OBSTRUCTION TO AIRFLOW CAUSED BY KINKING OF THE TUBE

Kinking, which could be a problem with the rubber Magill, occurs rarely with a standard Portex Magill, at least in adults. The modified Portex tube used in this study, even when subjected to maximum likelihood of kinking, never showed evidence of obstruction, which lends weight to the view that this problem has been overcome.

OBSTRUCTION TO AIRFLOW AT THE END OF THE TUBE

The end of the tube may become applied to the wall of the trachea, a blockage which can be relieved with a Murphy eye [15]. Making the bevel face backwards arguably increases the likelihood of this type of obstruction, particularly when there is fixed neck flexion (a notorious cause of difficult intubation). However, maximal neck flexion never caused serious impedance to airflow in our 96 cases. If in a larger sample obstruction did occur, then the simplest solution would probably be to push the tube in further. Blockage is likeliest at the point of maximal curvature of the airway, near the larynx; advancing the tube into the straight part should relieve it. This is not possible with the Oxford tube because of its fixed bend, but would be easy with our tube. If that worked, there would be no need for a Murphy eye.

OBSTRUCTION TO THE PASSAGE OF THE TUBE BETWEEN THE VOCAL CORDS

It is well known that if an introducer is used with a standard Magill tube, the end of the tube commonly becomes impacted at the cords; the Cardiff team [16] reported this in 50% of cases. To prevent this, Cossham [17] advocated rotating the tube 90° anticlockwise to make the bevel face backwards, and two surveys [12, 16] found this manoeuvre to be effective. Macintosh had a different solution, that is to alter the tube so that the bevel faced backwards. Both tubes used in this study had this feature and in all cases this was completely effective in preventing snagging at the cords. When the introducer was in place, entry of the tube was so smooth that it was hard to say at what point it traversed the cords. It is unfortunate that in his original report Macintosh did not explain why he had changed the direction of the bevel; had he done so it seems likely that this simple solution would have been adopted a long time ago. When a standard Magill tube is used with an introducer [12, 16] intubation appears to take longer than with our procedure, but firm conclusions are not possible because of differences in study design. A formal comparison would be instructive. Conclusions need to be confirmed in genuine cases of difficult intubation, but when research is hindered by the paucity of real cases, simulation provides a useful guide.

LEARNING EFFECT

The simulated difficult intubation drill is a straightforward technique that can be carried out by the novice; in some units it has been routine for many years to start teaching it as soon as the trainee is confident with simple intubations. We were surprised therefore to find a definite learning effect, even in those who are familiar with the drill. The case for the simulated difficult intubation drill, when it was originally proposed [7], suffered from the absence of precise data at that time on the incidence of difficult intubation. It is now known [18] that if care is taken with laryngoscopy, approximately 1.3% of cases are grade 3. A recent survey [19] found that anaesthetists generally perform approximately 200 intubations a year, so each will see two or three cases per year, on average. But, because of random variation (Poisson effect [20] 25% of anaesthetists will see 4–7 grade 3 cases in 200 consecutive intubations; at the opposite extreme, 26% will see only one, or none. Clearly those in the second group (the lower tail of the distribution), will have learnt little about difficult intubation in 1 year.

The learning effect that we have detected underlines these conclusions. The objection may be raised that the scatter of our results rules out exact inference. However, even if the true learning half-life were the lower 90% confidence limit of our data (fig. 3), nine intubations would be needed to become half-trained; not even the first group above (the upper tail of the distribution) will see that many grade 3 intubations in a year. The most probable inference from our data is a half-life of 15, which leads to the same conclusion, *a fortiori*.

If training is 50% complete after 15 intubations, then 30 is 75% of the way, and so on. Thirty intubations would seem a reasonable objective for a trainee before handling a high-risk case, such as a possible difficult intubation in a patient with a full stomach. Without such training the failed intubation rate in obstetrics, recently re-analysed [21], is likely to remain high.

Estimates of learning rates based on two individuals may not be typical for anaesthetists in general, but are unlikely to be seriously misleading. The principles underlying this measurement have been described in detail because it may prove useful for further studies. For example, it would be valuable to know if individual tuition increases the rate of learning, as shown for fibreoscopy [22]. With fibreoscopic intubation it is accepted that teaching must be done on patients who do not, strictly speaking, need fibrescopy. Hitherto it has not been obvious that the same applies to the handling of grade 3 cases, but from the evidence cited above any training strategy which relies on their random natural occurrence needs to be re-evaluated.

In summary, simulating the difficult intubation is a well-tried and trouble-free procedure for both training and research. The optimum design of the introducer and similar details require further study, but one factor seems clear, when choosing the right tube for use with an introducer, the new Portex tube is a strong contender. If it proves acceptable for difficult cases, it seems logical to use it for routine cases. There are advantages in safety, cost and convenience if the tube used for difficult intubations is the one we are most familiar with in everyday work.

Acknowledgements

We thank Mr C. Russell and Mr B. Greenfield, Portex Ltd, for their co-operation, and Dr R. S. Cormack for statistical help.

References

1. King TA, Adams AP. Failed tracheal intubation. *British Journal of Anaesthesia* 1990; **65**: 400–414.
2. McCarrol SM, Lamont BJ, Buckland MR, Yates APB. The gum-elastic bougie: old but still useful. *Anesthesiology* 1988; **68**: 643–644.
3. Macintosh RR. An aid to oral intubation. *British Medical Journal* 1949; **1**: 28.
4. Macintosh RR. A large bore endotracheal tube *Anaesthesia* 1950; **5**: 97–98.
5. Duckworth SI. The Oxford non-kinking endotracheal tube. Results of its use in about 18,000 cases *Anaesthesia* 1962; **17**: 208–214.
6. Jonas MM, West MRJ, Adams AP, Carli F. A new tube for grade 3 difficult intubations. *British Journal of Anaesthesia* 1993; **71**: 311P.
7. Cormack RS, Lehane J. Difficult intubation in obstetrics. *Anaesthesia* 1984; **39**: 1105–1111.
8. Nunn JF. *Applied Respiratory Physiology*, 1st Edn. London: Butterworths, 1969; appendix D (E in later edns).
9. Barlow RB. Line-fitting by least squares. In: *Biodata Handling with Microcomputers*. Cambridge: Elsevier, 1983: 94–99.
10. Snedecor GW, Cochran WG. *Statistical Methods*, 7th Edn. Iowa: Ames, 1980; 407–409.
11. Cormack RS, Mantel N. Doubt and certainty in statistics. *Journal of the Royal Society of Medicine* 1990; **83**: 136–137.
12. Nolan JP, Wilson ME. An evaluation of the gum-elastic bougie. *Anaesthesia* 1992; **47**: 878–881.
13. Ahearn RS. In: Nunn JF, Utting JE, Brown BR, eds. *General Anaesthesia*, 5th Edn. London: Butterworths, 1989; 669–670.
14. Royston P. Estimating departure from normality. *Statistics in Medicine* 1991; **10**: 1283–1293.
15. Murphy FJ, Two improved intratracheal catheters. *Anesthesia and Analgesia* 1941; **20**: 102–105.
16. Dogra S, Falconer R, Latto IP. Successful difficult intubation. *Anaesthesia* 1990; **45**: 774–776.
17. Cossham PS. Difficult intubation. *British Journal of Anaesthesia* 1985; **46**: 234.
18. Wilson ME, Spiegelhalter D, Robertson JA, Lesser P. Predicting difficult intubation. *British Journal of Anaesthesia* 1988; **61**: 211–216.
19. Williams KN, Carli F, Cormack RS. Unexpected difficult laryngoscopy; a prospective study in routine general surgery. *British Journal of Anaesthesia* 1991; **66**: 38–44.
20. Cormack RS. Predicting the obstetric work-load *Anaesthesia* 1984; **39**: 552–553.
21. Pilkington, S, Carli F, Dakin MJ, Romney M, De Witt KA, Doré CJ, Cormack RS. Increased Mallampati score in pregnancy. *British Journal of Anaesthesia* 1995; **74**: 638–642.
22. Smith JE, Fenner SG, King MJ. Teaching fibreoptic nasotracheal intubation with and without CCTV. *British Journal of Anaesthesia* 1993; 71: 206–211.

British Journal of Anaesthesia 1996; **76**: 680–684

Failed intubation revisited: 17-yr experience in a teaching maternity unit

L. HAWTHORNE, R. WILSON, G. LYONS AND M. DRESNER

Summary

We have reviewed 5802 Caesarean sections performed during general anaesthesia. Our use of general anaesthesia had decreased from 83% in 1981 to 23% in 1994. Despite this, the incidence of failed intubation has increased from 1 in 1984 to 1 in 250 in 1994. The problems associated with general anaesthesia in the obstetric population are increasing. Asians and African/Afrocaribbeans were represented disproportionately because of the increased use of general anaesthesia in these patients. Exposure of trainees to obstetric general anaesthetics has decreased by one-third. (*Br. J. Anaesth.* 1996; **76**: 680–684)

Key words
Intubation, tracheal. Anaesthesia, obstetric.

Failed tracheal intubation has been an important cause of anaesthetic-related maternal morbidity and mortality. In the North American closed claims study, difficult tracheal intubation and oesophageal intubation comprised 23% of damaging events associated with obstetric general anaesthesia [1]. In the Confidential Enquiries into Maternal Deaths in Great Britain for 1985–1987, four of six deaths directly attributable to anaesthesia were associated with failed tracheal intubation [2], but in the report for 1988–1990, only one of four deaths was a result of problems related to tracheal intubation [3]. Maternal deaths associated with anaesthesia at the beginning of the last decade comprised 13% of all direct maternal deaths, but by the end of the decade this had decreased to 2.2% [3,4]. Maternal mortality related to anaesthesia has probably reached its nadir, and it may be reasonable to suggest that efforts to reduce maternal mortality further might be more effective if directed at the management of haemorrhage. It has been suggested that the decrease in mortality is a result of the declining use of general anaesthesia [5]. In 1981 general anaesthesia was used for 83% of Caesarean sections in this unit, but by 1990 this had decreased to 33% (fig. 1); currently the incidence is 23%. Despite this, we have gained an impression that failure to intubate is no less common today than it was in 1985 when we last reviewed the performance of our unit [6]. Since 1985, we have expanded our data collection, introduced the laryngeal mask, pulse oximetry, capnography and a difficult intubation procedure (fig. 2). It seemed opportune that, at its 10th anniversary, we should revisit this topic, assess the impact of changes in clinical practice and verify our impressions.

Patients and methods

Between 1978 and 1994 we conducted a prospective audit of failure to intubate the trachea in our maternity unit. Failure to intubate was defined as intubation that was not accomplished with a single dose of suxamethonium, and therefore initiated the failed intubation drill (table 1). All women were visited after operation, the anaesthetist involved was interviewed and the information obtained was recorded. At the time of the postoperative visit, appropriate counselling was given, the significance of the incident for future anaesthesia explained and the case notes visibly annotated. The information recorded on our proforma is shown in table 2.

To support the review of these data, we sought additional information on subsequent anaesthetics by retrieval of case notes. The Birth Registers for each year were examined to provide details of the number of Caesarean sections performed, the percentage performed during general anaesthesia, whether the procedure was elective or emergency and time of operation. This was divided into three groups according to time of day and week: group 1, 08:00–17:00; groups 2, 17:00–21:00; group 3, 21:00–08:00 and the weekend. During normal working hours (group 1), theatre staff were designated to the obstetric theatre and consultant anaesthetists were available to oversee the work of trainees. In group 2 (17:00–21:00), theatre staff were available and medical staff cover was provided by the duty doctors for that day. In group 3 (21:00–08:00 and weekends), midwives provided the nursing staff cover, an operating department assistant was available from the general theatres in another section of the hospital and medical cover was again provided by the duty doctors.

Data collected were collated and presented against the background unit activity.

Results

Between 1978 and 1994, 5802 Caesarean sections were performed during general anaesthesia; there

---

L. A. HAWTHORNE, FRCA, R. C. WILSON, MRCP, FRCA, G. LYON, FRCA, M. DRESNER, FRCA, Department of Anaesthesia, St James's University Hospital, Beckett Street, Leeds LS9 7TF. Accepted for publication: December 23, 1995.

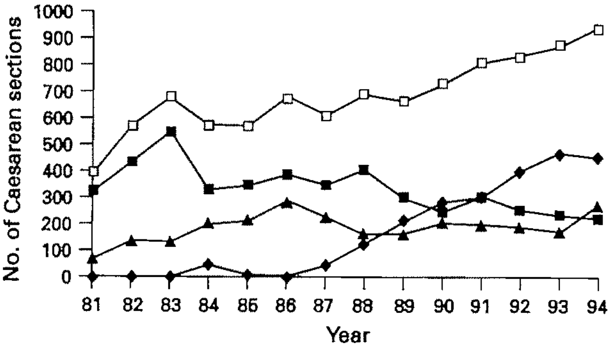


Figure 1 Number of obstetric anaesthetics from 1981 to 1994. ◆ = Spinal anaesthesia, ■ = general anaesthesia, ▲ = extradural anaesthesia, □ = total number.

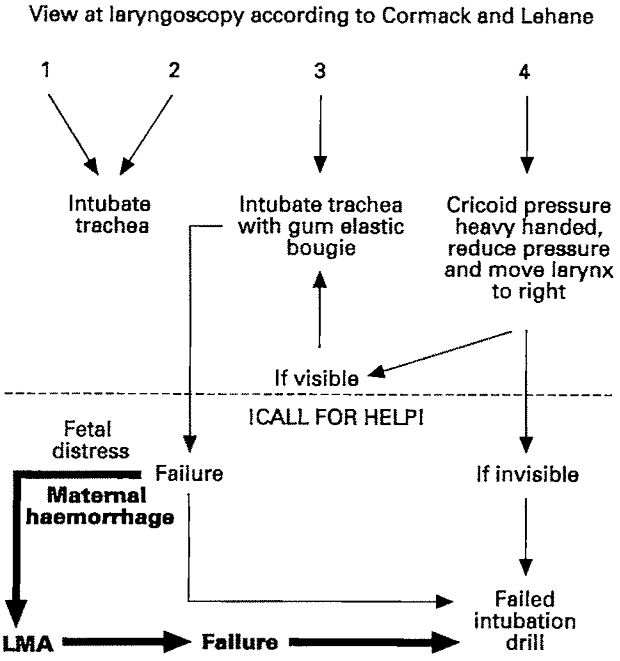

View at laryngoscopy according to Cormack and Lehane
1
2
3
4
Intubate trachea
Intubate trachea with gum elastic bougie
Cricoid pressure heavy handed, reduce pressure and move larynx to right
If visible
!CALL FOR HELP!
Fetal distress
Failure
Maternal haemorrhage
If invisible
Failed intubation drill
LMA
Failure

Figure 2 Difficult intubation procedure.

Table 1 Failed intubation drill at St James's University Hospital maternity unit

Management procedure

A failed intubation is an intubation that cannot be accomplished with a single dose of suxamethonium

(1) Do not give another dose of suxamethonium
(2) Summon all hands
(3) Turn patient on left side, head down position
(4) Give 100% oxygen
(5) If ventilation is difficult, release cricoid pressure
(6) Summon on-call consultant
(7) Support until spontaneous breathing returns
(8) Discuss further management with consultant

were 23 (0.4%) failures to intubate the trachea. Our incidence of failed tracheal intubation had increased from 1 in 300 general anaesthetics in 1984 to 1 in 250 in 1994. Patient data are shown in table 3. Thirteen (56%) of the patients were white; there were five (22%) Asian patients and five (22%) were of African/Afrocaribbean origin.

Table 2 Patient details and failed intubation data

Age
Weight
Height
Ethnic origin
Grade of anaesthetist
Time of operation
Urgency: Elective
  Emergency
Previous/subsequent intubation
Preoperative assessment
Intubation details
Intubation aids
Ease of bag and mask ventilation
Management
Obstetric indication
Outcome
Postoperative findings: Head and neck movements
  Jaw movements
  Receding jaw
  Teeth
Postoperative investigations

Table 3 Patient characteristics (mean (SD) [range])

Age (yr)	30	[20–42]
Weight (kg)	72.5 (17.1)	[45.6–106]
Height cm	157 (7)	[146–167]

GRADE OF ANAESTHETIST

The grade of anaesthetist was a senior house officer or registrar in 18 (78%) of the 23 incidents, a senior registrar or consultant anaesthetist in three (13%), and in two cases (9%) the anaesthetist was not named. The distribution workload of obstetric general anaesthesia in our unit is summarized in table 4.

TIME OF OPERATION

Sixteen (69%) of 23 failures occurred in group 3; five cases (22%) occurred in group 1, and two (9%) in group 2. This was compared with a typical 12-month period in table 5.

URGENCY

In two instances (9%) surgery was elective, emergency surgery was performed in 20 (87%), and there was one planned emergency (4%). This latter case was performed out of hours on a woman who was booked to have an elective Caesarean section but was

Table 4 Obstetric general anaesthetics from 1987 to 1994 and grade of anaesthetist (expressed as %). Grade of anaesthetist refers to the first anaesthetist. The percentage of consultant general anaesthetics has decreased in recent years as a result of increased teaching of trainees in the performance of obstetric general anaesthetics

	Year							
	87	88	89	90	91	92	93	94
Consul.	26	23	26	23	19	23	16	14
SR	11	10	8	13	13	14	14	18
Reg.	43	42	50	46	36	31	42	38
SHO	17	23	16	18	31	30	28	30
Other	3	2	0	0	1	2	0	0

Table 5 Time of operation and urgency in failed intubation series and a typical 12-month period. * Includes one planned emergency

	Failed intubation series	12-month period (1993)
Group 1 (08:00–17:00)	5 (22%)	726 (84%)
Group 2 (17:00–21:00)	2 (9%)	33 (4%)
Group 3 (21:00–08:00 + weekend)	16 (69%)	108 (12%)
Elective	2 (9%)	483 (56%)
Emergency	21 (91%)*	384 (44%)

admitted in labour. Elective operation normally comprises 56% of the total Caesarean sections (table 5).

PREOPERATIVE ASSESSMENT

All patients had been seen by an anaesthetist before operation but difficulty in tracheal intubation was anticipated in only one-third. Of these, two patients were noted to have a short neck and four had a receding jaw, two of whom also had prominent teeth. When recorded, Mallampati score [7] was either grade II or III. In 14 patients (61%) the trachea had been intubated successfully either before or subsequent to this.

LARYNGOSCOPY

At attempted intubation the Cormack and Lehane grade was described as 3 (only epiglottis visible) in 15 patients [8]. In one patient there was severe masseteric spasm and mouth opening was impossible. This patient was referred for muscle biopsy and suspected malignant hyperthermia; unfortunately she failed to attend follow-up appointments and eventually declined further investigation. Laryngeal oedema was reported in six patients; of these two had pre-eclampsia and another two had generalized oedema but were normotensive and had no evidence of proteinuria.

MANAGEMENT

Ventilation with a bag and face mask was described as difficult in seven patients (30%) and impossible in two (9%). Eighteen patients were allowed to waken and a regional technique was used; extradural anaesthesia in 10 (43%), spinal in five (22%) and combined spinal–extradural in three (13%). In three patients a laryngeal mask was inserted; in two the lungs were difficult to ventilate with a bag and face mask. Laryngeal oedema was noted in all three patients, two of whom had pre-eclampsia. Cricoid pressure was maintained and they all resumed spontaneous respiration. In a fourth patient a laryngeal mask was inserted but oxygenation proved impossible. It was removed and ventilation with a face mask was used until the patient resumed consciousness. This patient was a large woman (105 kg) with a short neck; she was oedematous but the cords were not seen.

One patient in whom ventilation was described as impossible had an attempted minitracheostomy which failed and was managed subsequently with a face mask and airway when spontaneous respiration unexpectedly resumed. In another case the patient's trachea was subsequently intubated by the same anaesthetist after the failed intubation drill had been instigated, as a good view of the cords was obtained in the left lateral position.

OUTCOME

Despite the indications being fetal distress in seven cases, outcome was good for mother and baby in all but one patient. In the seventh, the mother's outcome was good but her twins had cerebral damage.

FOLLOW-UP

All patients were visited after operation and examined, with particular reference to head, neck and jaw movements, mandibular size and awkward or prominent teeth. Postoperative examination details were not recorded for four patients. The commonest postoperative finding on examination was the presence of a receding jaw (nine patients) followed by limited mouth opening (seven patients); five patients had both these abnormalities. Prominent or awkward teeth were present in five patients, four of these also had a receding jaw. Limited head and neck movements were found in only three patients, associated with limited mouth opening in each case. One patient had all of these findings.

INVESTIGATIONS

Postoperative investigations included indirect laryngoscopy (six patients) and radiographic examination of the cervical spine (five patients) and mandible (five patients). In recent years we have excluded indirect laryngoscopy and x-rays from our regimen.

Discussion

Failed tracheal intubation is well documented in the obstetric population, with an incidence almost eight times higher than in other groups [9]. Against a relative background of declining use of general anaesthesia, the incidence of failure to intubate has increased in our maternity unit, from 1 in 300 general anaesthetics in 1984, to 1 in 250 in 1994. The working practice in our unit mirrors that of the nation as a whole [10]; an increase in the number of Caesarean sections, an increase in the percentage performed under regional anaesthesia and no change in the total number of obstetric general anaesthetics. The national mortality has decreased to approximately 1 in 100000 Caesarean sections, but in common with most other units, we have no data to compare with this. On the other hand, our series has shown an increase in morbidity (failure to intubate). Whether or not this also reflects a national trend is

Table 6 Number of Asian and non-Asian patients undergoing Caesarean section and method of anaesthesia from 1992 to 1994. Chi-square = 73.14, significant at $P < 0.0001$ (for proportion of Asians undergoing general anaesthesia (GA)

	1992	1993	1994
Asians			
GA	45 (64 %)	38 (43 %)	39 (44 %)
Regional	25 (36 %)	50 (57 %)	50 (56 %)
Total	70	88	89
Non-Asian			
GA	202 (27 %)	192 (25 %)	179 (21 %)
Regional	560 (73 %)	587 (75 %)	668 (79 %)
Total	762	779	847
Total	832	867	936

open to question as there are no national data available.

In the Confidential Enquiry into Maternal Deaths for 1976–1978 there was an inference that dark-skinned patients were over-represented [11]. A disproportionately large number (46 %) of patients in our series were Asian or Black, while this group comprised less than 20 % of all patients delivering in our obstetric unit. Since the introduction of pulse oximetry, cyanosis is no longer undetected. In a review of maternal deaths in Michigan, inability to establish airway patency was the main cause of anaesthesia-related death in recent years; 13 of 15 deaths occurred in black patients and the three cases of failed tracheal intubation which resulted in fatality were in this group [12]. Why should Asian and African patients represent such a large proportion in our series? This could be because of a higher incidence of Caesarean section in this group, but we have not found this to be the case. A more likely explanation is the increased use of general anaesthesia. In a recent audit (1994) of the Asian population in our unit, 39 of 89 (44 %) of those undergoing Caesarean section had a general anaesthetic compared with 179 of 847 (21 %) in non-Asians. Asian women were 2.1 (95 % confidence interval 1.8–2.4) times more likely to have a general anaesthetic for Caesarean section in our unit than non-Asians (table 6). Preference for general anaesthesia may be a result of language barriers, although 50 % of these patients were African/Afrocaribbean who tend to be English speaking. Cultural background and peer pressure may also contribute. To reduce the risk of failed intubation in Asians and African/Afrocaribbeans, we must attempt to modify our attitudes to regional anaesthesia.

Potential risk factors known to be associated with difficult tracheal intubation include short neck, obesity, missing maxillary incisors, protruding maxillary incisors, single maxillary incisor and receding mandible [13]. The most frequently occurring anatomical findings in our review were receding jaw and limited mouth opening, followed by awkward or prominent teeth. Despite these findings, it should be noted that in one-third of patients, clinical examination was normal, and nearly two-thirds had undergone intubation successfully on another occasion, therefore acting as their own controls. As bony structures are unchanged from the non-pregnant state, any contributory factor presumably resides with the soft tissues. During pregnancy there is capillary engorgement of the nasopharynx and larynx. Total body water increases and generalized oedema may occur in patients who are normotensive with normal renal function. Oedema is thought to be caused by the effect of oestrogen on the ground substance of connective tissue. Laryngeal oedema has been recorded in patients without pre-eclampsia in whom strenuous physical effort associated with labour has resulted in increased venous pressure in the head and neck [9]. We failed to demonstrate laryngeal oedema as a common contributory factor. This may be because of the fact that patients were referred for an ENT opinion when any oedema had subsided. In our review the commonest finding at laryngoscopy was Cormack and Lehane grade 3.

We have commented on the anatomical and physiological factors that can result in failure to intubate, but there are environmental factors on the labour ward that may contribute. The majority of cases of failed intubation were emergencies, occurring out of normal working hours and involved trainees (senior house officers and registrars) working with "skeleton" theatre staff. Experience of general anaesthesia for Caesarean section is diminishing, especially among trainees. The annual mean individual case load of obstetric general anaesthetics in these grades has decreased in the past decade, from 18 in 1984 to 12 in 1994. In 1984 there were 230 obstetric general anaesthetics performed; this incidence had increased to 258 in 1994. This implies that reduced exposure to general anaesthesia in obstetrics is because of an increased number of trainees rather than a decreased number of general anaesthetics. As we have reported, the commonest Cormack and Lehane grade was 3. Any procedure must teach the management of intubation when Cormack and Lehane grade 3 is found at laryngoscopy. We have aimed to do this, although we have not been able to provide simulation in routine operating lists as suggested [8]. Other factors which may be relevant in the difficult obstetric intubation include thoracic lift from a badly placed wedge and over-enthusiastic cricoid pressure. This probably explains why tracheal intubation was achieved successfully in the left lateral position, but impossible when supine, in one of the patients in our review.

In only one patient was neonatal outcome poor. This may have been secondary to antepartum factors and not associated with the delay in delivery because of failed intubation. In one of the patients in our review, oxygen saturation was recorded as low as 17 %. Despite this, both mother and neonate had a favourable outcome. This is the only documented case of severe hypoxia in our review. We believe that in the event of failure to oxygenate the lungs of the mother, further attempts at maternal resuscitation should persist. There is now evidence to suggest that neonatal outcome is more dependent on chronic hypoxia and other antepartum factors [14] rather than the acute anoxia associated with temporary inability to ventilate the lungs of the mother. Delivery of the neonate should be expedited, however, if maternal cardiac arrest is imminent, as this provides the best chance of neonatal survival and maternal resuscitation is usually impossible with a term fetus *in utero*.

Since the last review of failed tracheal intubations in our unit in 1984, enthusiasm for postoperative investigations has waned. Indirect laryngoscopy was reported as normal in all patients during the past 17 yr. Although cervical spine radiographs yielded abnormalities in two patients in the previous review [6] we now feel that anatomical factors are less important.

In the last review of failure to intubate in our unit, the laryngeal mask airway had not gained widespread use. Recently however, the laryngeal mask airway has been used when intubation has not been possible. It was interesting that all three patients in whom successful use of the laryngeal mask was used had laryngeal oedema. Two of these patients had undergone tracheal intubation on a previous occasion and all three had normal postoperative findings. This would suggest that the use of the laryngeal mask in this clinical situation may be particularly justified. The importance of maintaining cricoid pressure should be emphasized and gastric emptying with a stomach tube should be considered. Although protection against aspiration is not ensured, the laryngeal mask can help maintain oxygenation in patients whose lungs are difficult to ventilate with a bag and face mask or where life-threatening haemorrhage is imminent and surgery must be continued. The successful use of the laryngeal mask for failed intubation in Caesarean section has been reported previously by McClune, Regan and Moore [15] and Chadwick and Vohra [16]. As suggested by Benumof [17], we have introduced a difficult intubation regimen, but we have not seen a reduction in failure to intubate. We have now modified our difficult intubation regimen to include the laryngeal mask airway (fig. 2).

References

1. Chadwick HS, Posner K, Caplan R, Ward RJ, Cheney FW. A comparison of obstetric and non-obstetric malpractice claims. *Anesthesiology* 1991; **74**: 242–249.
2. Report on Confidential Enquiry into Maternal Deaths in Great Britain in 1984–1987. London: HMSO, DHSS 1991.
3. Report on Confidential Enquiry into Maternal Deaths in Great Britain in 1988–1990. London: HMSO, DHSS 1994.
4. Report on Confidential Enquiry into Maternal Deaths in England and Wales in 1982–1984. London: HMSO, DHSS 1989.
5. Thomas TA. Maternal mortality. *International Journal of Obstetric Anaesthesia* 1994; **3**: 125–126.
6. Lyons G. Failed intubation. Six years' experience in a teaching maternity unit. *Anaesthesia* 1985; **40**: 759–762.
7. Mallampati SR, Gatt SP, Gugino LD, Desai SP, Waraksa B, Freiburger D, Liu PL. A clinical sign to predict difficult intubation: a prospective study. *Canadian Anaesthetists Society Journal* 1985; **32**: 429–434.
8. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; **39**: 1105–1111.
9. King TA, Adams AP. Failed tracheal intubation. *British Journal of Anaesthesia* 1990; **65**: 400–414.
10. Brown GW, Russell IF. A survey of anaesthesia for caesarean section. *International Journal of Obstetric Anaesthesia* 1995; **4**: 214–218.
11. Report on Confidential Enquiry into Maternal Deaths in England and Wales in 1976–1978. London: HMSO, DHSS 1982.
12. Endler GC, Mariona FG, Sokol RJ, Stevenson LB. Anesthesia-related maternal mortality in Michigan, 1972 to 1984. *American Journal of Obstetrics and Gynecology* 1988; **159**: 187–193.
13. Rocke DA, Murray WB, Rout CC, Gouws E. Relative risk analysis factor associated with difficult intubation in obstetric anesthesia. *Anesthesiology* 1992; **77**: 67–73.
14. Adamson SJ, Alessandri LM, Badawi N, Burton PR, Pemberton PJ, Stanley F. Predictors of neonatal encephalopathy in full term infants. *British Medical Journal* 1995; **311**: 598–602.
15. McClune S, Regan M, Moore J. Laryngeal mask airway for caesarean section. *Anaesthesia* 1990; **45**: 227–228.
16. Chadwick IS, Vohra A. Anaesthesia for emergency caesarean section using the Brain laryngeal airway. *Anaesthesia* 1989; **44**: 261–262.
17. Benumof JL. Management of the difficult adult airway. *Anesthesiology* 1991; **75**: 1087–1110.

British Journal of Anaesthesia 1996; **76**: 685–693

Haemodynamic responses to incision and sternotomy in relation to the auditory evoked potential and spontaneous EEG†

N. A. M. DE BEER, J. C. VAN HOOFF, P. J. M. CLUITMANS, H. H. M. KORSTEN AND R. J. E. GROULS

Summary

We investigated the effect of incision and sternotomy on the auditory evoked potential (AEP) and EEG, to try to predict a haemodynamic response to incision or sternotomy using the AEP and EEG in 41 patients undergoing cardiac surgery during propofol and alfentanil anaesthesia. The AEP and EEG were recorded before incision, between incision and sternotomy, and after sternotomy. Peak latencies and amplitudes of AEP peaks V, Na, Pa, Nb, Pb and Nc were determined. From the EEG the median, spectral edge and peak power frequencies, and percentages of delta, theta, alpha and beta power were calculated. Each patient was classified as responsive, equivocally responsive or unresponsive to incision or sternotomy based on increase in arterial pressure and heart rate on incision and sternotomy. Before incision, Nb and Pb latency and propofol concentration were higher for unresponsive patients but heart rate and median frequency before incision were lower. After sternotomy, Pa and Nb amplitude, peak power frequency and percentage alpha power were higher, and percentage theta power lower for responsive patients. Pa latency was higher after sternotomy for unresponsive patients. Using a combination of heart rate, arterial pressures and features derived from the AEP (all recorded before incision), the occurrence of a response to incision could be predicted in individual patients with a sensitivity of 85%, positive predictive accuracy of 63% and total accuracy of 72%. We conclude that AEP are more sensitive to pain stimuli than spectral features of the spontaneous EEG. In addition, the AEP may help in predicting inadequate anaesthesia. (*Br. J. Anaesth.* 1996; **76**: 685–693)

Key words

Monitoring, evoked potentials. Monitoring, electroencephalography. Cardiovascular system, effects. Surgery, cardiovascular.

The purpose of general anaesthesia is to provide a state of analgesia, unconsciousness, relaxation and homeostasis in the surgical patient. Because different patients may react differently to similar concentrations of anaesthetic agent, an objective measure of analgesia and unconsciousness is desired. Results from previously published studies suggest that features derived from the spontaneous electroencephalogram (EEG) [1, 2] or from auditory evoked potentials (AEP) [3–8] may be useful for monitoring the effects of anaesthesia.

Clinically, adequacy of anaesthesia may be evaluated by observing movement or an increase in arterial pressure or heart rate in response to a noxious stimulus. Attempts to use the EEG to predict such a response showed that features derived from the EEG may predict the presence or absence of movement in response to a noxious stimulus with an accuracy of 77–92% [1, 2, 9]. A study by Thornton and colleagues showed that the effects of anaesthesia on the AEP are reversed by pain stimuli [3], but the effect of surgery on the AEP was not different for patients showing a haemodynamic response compared with those in which no such response was present [10]. Also, no attempt at predicting the occurrence of a response to surgery was made, probably because of the small number of patients in that study.

In this study we have used absence of a haemodynamic response to incision and sternotomy as an indication for adequate anaesthesia. The hypotheses underlying our study are: features in the AEP and EEG are sensitive to pain stimuli, in this case incision and sternotomy; patients who respond to incision, sternotomy, or both, with a haemodynamic response show different AEP and EEG features than patients who do not respond, whereas such a difference does not exist in haemodynamic variables measured before incision or sternotomy; the presence or absence of a haemodynamic response is related to plasma concentrations of the administered anaesthetics; and the occurrence of a haemodynamic response to incision can be predicted using features or a combination of features derived from the AEP

N. A. M. DE BEER, MSC, P. J. M. CLUITMANS, PHD, Department of Medical Electrical Engineering, Eindhoven University of Technology, PO Box 513, 5600 MB Eindhoven, The Netherlands. J. C. VAN HOOF, MSC, Section of Physiological Psychology, Tilburg University, PO Box 90153, 5000 LE Tilburg, The Netherlands. H. H. M. KORSTEN, MD, PHD, R. J. E. GROULS, PHARMD, Catharina Hospital, PO Box 1350, 5602 ZA Eindhoven, The Netherlands. Accepted for publication: December 13, 1995.

† Presented in part at the Third International Symposium on Memory and Awareness in Anaesthesia, Rotterdam, The Netherlands, June 8–10, 1995.

and EEG, together with measurements of heart rate and arterial pressure obtained before incision.

Patients and methods

The study was performed at the Catharina Hospital Eindhoven, after obtaining approval from the local Medical Ethics Committee and informed patient consent. We studied 41 patients (34 male) aged 38–74 yr (mean 59 yr) undergoing cardiac surgery. Two patients were undergoing aortic valve replacement and 39 coronary artery bypass grafting. Patients were premedicated approximately 2 h before surgery with morphine 10 mg s.c. Anaesthesia was induced with a loading dose of propofol 2 mg kg^{-1} i.v. and alfentanil 100 µg kg^{-1} i.v. given over 12 min. After these 12 min, anaesthesia was maintained with propofol 8 mg kg^{-1} h^{-1} and alfentanil 4 µg kg^{-1} min^{-1} for 10 min, then propofol 6 mg kg^{-1} h^{-1} and alfentanil 3 µg kg^{-1} min^{-1} for 10 min and finally propofol 4 mg kg^{-1} h^{-1} and alfentanil 2 µg kg^{-1} min^{-1} for the remainder of the operation. Pancuronium 8 mg was used to facilitate tracheal intubation.

RECORDINGS

The raw EEG was recorded from Cz to A1 and from Cz to A2, each referenced to Fpz. Electrode impedance was maintained below 3 kΩ; typically electrode impedance was 1.5 kΩ (measured at 20 Hz). The EEG was amplified and filtered at 5–1500 Hz (−3 dB cut-off) using a Nicolet HGA-200A preamplifier and a Nicolet NIC-501A amplifier/filter. The EEG was sampled at 5 kHz with a resolution of 12 bit and stored on hard disk, using a LabMaster AD converter and an IBM-type 486 33 MHz personal computer. Auditory stimulation for the evoked potentials was performed with monaural 100-µs rarefaction clicks at 75 dB SpL, and contralateral white masking noise at 45 dB SpL. Clicks and noise were produced using a Nicolet 1007 stimulus controller and delivered to the patient through Nicolet Tip-10 earphones. Clicks were delivered with random interstimulus intervals, according to a Poisson distribution, with an average stimulation rate of 80 clicks per second. An important implication of using this distribution for random presentation of stimuli is that the effects of interfering stimuli are equally distributed over the entire sweep, independent of sweep length [11–13]. This results in a smoothing of the effect of interfering stimuli. For analysis of the AEP, we chose a sweep length of 270 ms to ensure that component Nc could be detected if present.

Auditory evoked potentials were recorded starting 10 min before the first incision until 10 min after sternotomy. After automatic detection and removal of sweeps containing artefacts [14], AEP were averaged over the period starting 10 min before the first incision to the end at incision, from incision to sternotomy and from the start of sternotomy until 10 min after the end of sternotomy. From the resulting averages the latency and amplitude of brain stem peak V and of middle latency peaks Na, Pa, Nb, Pb and Nc were determined. For this purpose, we used a combination of automatic recognition of MLAEP peaks by an artificial neural network [Van Gils and Cluitmans, Locating characteristic peaks in auditory evoked potentials using artificial neural networks, submitted] and evaluation by a human observer. The neural network assessed the location of the peaks, and the visual evaluation consisted of checking if the observer agreed with the choice of the neural network in "difficult" cases. In most cases, this meant checking if an auditory response was present at all. This is because the neural network always provides an answer, even in waveforms where no clear brain stem response is present.

Brain stem peak V was used to check if a response was present: if peak V could not be determined, the entire AEP was not used in further processing. The AEP was also not used in further processing if, because of the occurrence of artefacts, the total number of sweeps in the resulting average was less than 3000 (corresponding to a net recording time of 38 s).

The raw EEG recorded for AEP averaging was also used for spectral analysis, using the CCSA software package developed in our group [15]. Before calculation of the spectra, the EEG was digitally low-pass filtered at 32 Hz, using a 69-point moving average filter. Detection and rejection of epochs containing artefacts was done using the same algorithm as used for detecting artefacts in the AEP. Spectra were calculated from 8-s epochs, using an overlap of 2 s between epochs, and applying a Blackman time window to prevent spectral leakage. Features derived from the calculated spectra were median, 95% spectral edge and peak power frequency, and percentage delta (0–4 Hz), theta (4–8 Hz), alpha (8–14 Hz) and beta (above 14 Hz) power. The resulting spectral features for each recording were averaged over the same period as the AEP, to have one set of EEG features for each set of AEP features. If the occurrence of artefacts caused the total number of epochs included in this averaging to be lower than 6 (corresponding to a net recording time of 38 s), that set of EEG features was not used in further processing.

Because the raw EEG was high-pass filtered at 5 Hz to enhance the quality of the AEP recordings, the calculated spectral features are higher than the values reported in the literature necessary for surgical anaesthesia [16, 17], especially for median and peak power frequency. Percentage delta power is lower in our study. Although the filter removes a large part of the delta activity, we considered it valid to include percentage delta power in the analysis, because the filter is not able to remove all delta activity. This allows for trends in delta power to be observed, but possibly affects the significance of any changes in delta power, because these changes are less clear.

OCCURRENCE OF A RESPONSE TO INCISION AND STERNOTOMY

Values of systolic, diastolic and mean arterial pressures (SAP, DAP and MAP) and heart rate (HR) were obtained 1 min before and after incision, and 1 min before and after sternotomy. Changes in arterial pressure and heart rate (ΔSAP, ΔDAP, ΔMAP, ΔHR) were classified into one of four categories: ΔSAP, ΔDAP, ΔMAP were classified as + + + if the increase was larger than 20 mm Hg, + + if the increase was larger than 10 mm Hg, + for increases larger than 3 mm Hg and − if there was a change smaller than 3 mm Hg or a decrease; ΔHR was classified as + + if the increase was larger than 10 beat min^{-1}, + for an increase larger than 3 beat min^{-1} and − if there was a change smaller than 3 beat min^{-1} or a decrease in heart rate.

Based on the classifications for ΔSAP, ΔDAP, ΔMAP and ΔHR, each patient was classified as responsive (+ +), equivocal (+) or unresponsive (−) to incision or sternotomy according to the following criteria: if either ΔSAP, ΔDAP or ΔMAP was classified as + + +, the patient was classified as responsive; if ΔSAP, ΔDAP and ΔMAP were all classified as + +, the patient was also classified as responsive; if all but one of ΔSAP, ΔDAP and ΔMAP were classified as + +, the remaining pressure was classified as +, and ΔHR was classified as +, the patient was also classified as responsive; if no variable had a classification higher than +, the patient was classified as unresponsive. All other patients were classified as showing an equivocal response. This classification into response groups was done twice for all patients: once for the response to incision, and once for the response to sternotomy. A threshold of 3 mm Hg and 3 beat min^{-1} was chosen to prevent noise in arterial pressure and heart rate measurements from influencing the resulting patient classification. However, choosing a threshold of 0 mm Hg and 0 beat min^{-1} did not change this classification.

For those patients who responded unequivocally to incision, the anaesthetic record was checked to see if and how the anaesthetist had treated this response to incision, because such a treatment may have affected the response to sternotomy.

PROPOFOL AND ALFENTANIL CONCENTRATIONS

Immediately after sternotomy, an arterial blood sample was obtained. These samples were analysed by the hospital pharmacy for concentrations of propofol, using high performance liquid chromatography with fluorometric detection. Plasma concentrations of alfentanil were quantified by a validated radioimmunoassay [18] at the Pharmacokinetics Laboratory of the Janssen Research Foundation, Beerse.

STATISTICAL ANALYSIS

For all comparisons between groups of patients for response to incision or sternotomy, a Kruskal–Wallis test with a significance level of 5% was used. For those features for which the Kruskal–Wallis test indicated a statistically significant difference between groups, groups were compared pairwise. For these pairwise comparisons we used a Wilcoxon test with Bonferroni correction, with a significance level of 5%. This implies that a difference between two groups was considered to be statistically significant if the P value resulting from the Wilcoxon test was smaller than 0.05/(number of comparisons) = 0.025. The number of comparison was two, because we always compared responsive with unresponsive and equivocally responsive patients, or we compared unresponsive with responsive and equivocally responsive patients. We used non-parametric tests, because of the low numbers of observations in the different groups. For comparisons of AEP and EEG features between the three recording periods, we also used a Kruskal–Wallis test, and a Wilcoxon test with Bonferroni correction for pairwise comparisons.

Group means tested for statistically significant differences were: AEP and EEG features for each of the three recording periods, averaged over all patients; propofol and alfentanil concentrations for each of the three patient groups for response to incision and response to sternotomy; AEP and EEG features for each of the three patient groups for response to incision and response to sternotomy, for each recording period; and SAP, DAP, MAP and HR before incision and before sternotomy, for each of the three patient groups for response to incision and response to sternotomy.

PREDICTING THE RESPONSE TO INCISION

A discriminant analysis was used to examine if it is possible to predict the occurrence of a response to incision. Based on observations of arterial pressures, HR, AEP and EEG features, a discriminant function was estimated that optimally separates groups of responsive, equivocally responsive and unresponsive patients. Estimation of the optimal discriminant function was performed several times, using different sets of the available features from all patients. First, we attempted to predict the response to incision using only the available observations for SAP, DAP, MAP and HR measured before incision, because this information is conventionally available to the anaesthetist. In subsequent analyses, more variables were included for estimation of the discriminant function. These added variables were median, spectral edge and peak power frequency, and percentage delta, theta, alpha and beta power derived from the EEG in the second cycle, latencies and amplitudes of peaks V, Na, Pa, Nb, Pb and Nc from the AEP in the third cycle, and finally the variables derived from both the AEP and the EEG in the fourth cycle. In each cycle, the discriminant analysis calculated the best linear combination of features from the total available data set by stepwise selection of variables, to optimally separate the three response groups. The resulting discriminant function was tested after each cycle to see if its predictions agreed with the actual occurrence of a response. Because in this study we have only a limited account of data available, we used the leave-one-out method for cross validation. This implies that, when we have n data points, the discriminant function is calculated from $n-1$ data points and subsequently tested on the one remaining datum point. This is repeated n times so that each datum point is used exactly once for testing.

The performance of the resulting discriminant function in each cycle was assessed in terms of total

Table 1 Schematic representation of the predictions of the discriminant function. The number of cases in actual response group *i* and predicted response group *j* are denoted by X*ij*

	Predicted response		
	0	1	2
Actual response			
0	X00	X01	X02
1	X10	X11	X12
2	X20	X21	X22

accuracy, sensitivity and positive predictive accuracy. Using the schematic representation of the predictions of the discriminant function in table 1, total accuracy is defined as the actual percentage of correct predictions:

$$\text{Accuracy} = \frac{X00 + X11 + X22}{\sum_{i,j} Xij}$$

Sensitivity indicates how well the discriminant function is able to predict the occurrence of a response. The definition we used for sensitivity indicates the probability that the actual occurrence of a response or an equivocal response to incision is not underestimated by the discriminant function:

$$\text{Sensitivity} = \frac{X11 + X12 + X22}{\sum_j X1j + \sum_j X2j}$$

Positive predictive accuracy indicates what percentage of cases predicted to show a response is indeed showing a response. The following definition of positive predictive accuracy gives the probability that the prediction of a response or an unequivocal response to incision is not an overestimation of the actual response:

$$\text{Positive predictive accuracy} = \frac{X11 + X21 + X22}{\sum_i Xi1 + \sum_i Xi2}$$

Results

The first incision occurred at a mean time of 32 (SD 4) min after induction and sternotomy occurred 36 (5) min after induction. We obtained auditory evoked potentials from 39 patients. In 38 of these we also obtained a blood sample immediately after sternotomy. We could not reliably record an AEP in each period in all patients. Before incision the total number of recordings from which both AEP features and EEG spectral features could be reliably obtained was 32. Between incision and sternotomy this number was 6, and after sternotomy we obtained recordings from 32 patients.

The mean values of AEP peak latencies and amplitudes and of EEG spectral features for each of the three measurement periods are presented in figure 1. In this and other figures and tables, only contralateral results are presented. The ipsilateral results are comparable, but we preferred contralateral over ipsilateral because there were more observations available for the contralateral recordings. The amplitudes of peaks Nb and Pb were significantly increased ($P = 0.0464$ and 0.0170, respectively) during the period between incision and sternotomy. Pairwise comparisons between recording periods revealed that the group means of recordings before and after incision were significantly different. There was also a significant effect in median frequency ($P = 0.0421$), but pairwise comparisons revealed no significant differences between recording periods.

Three patients responded unequivocally to the first incision and four patients responded unequivocally to sternotomy. All three patients who responded to incision did not respond to sternotomy. One of these had been given ketensine 5 mg, approximately 1 min before sternotomy. The other two were treated with an increased dose of propofol but, according to the anaesthetic record, only several minutes after sternotomy. Of the four patients who responded to sternotomy, two had equivocally responded to the first incision, the other two had not responded. The number of responsive patients for the different conditions is summarized in table 2.

Table 3 summarizes which variables showed significantly different group means between responsive, equivocally responsive and unresponsive patients. There were no statistically significant differences in AEP and EEG features obtained between incision and sternotomy between patient groups for response to incision, and between patient groups for response to sternotomy. In the next sections the effects on AEP latencies before incision, AEP amplitudes after sternotomy and EEG features in these periods are discussed in more detail.

There were no statistically significant differences in mean SAP, DAP or MAP recorded before incision between patient groups for response to incision. HR before incision was significantly different ($P = 0.0451$) between patient groups: 59.7 (SD 9.6) beat min^{-1} for patients unresponsive to incision, 66.0 (5.0) beat min^{-1} for patients equivocally responsive to incision and 77.0 (12.8) for responsive patients. However, pairwise comparisons revealed no statistically significant differences between groups. There were no statistically significant differences in haemodynamic variables recorded before sternotomy between patient groups for the response to sternotomy.

Mean propofol and alfentanil concentrations for the different response groups are shown in table 4. These were calculated using data only from those patients for whom AEP and EEG data were available. Although concentrations of alfentanil were lower for patients responsive to sternotomy, this effect was not significant. There were also no statistically significant differences in concentrations of alfentanil between patient groups for response to incision. There was a significant overall effect in concentrations of propofol for response to incision ($P = 0.0258$). Pairwise comparisons showed that patients unresponsive to incision had significantly greater propofol concentrations than patients who responded equivocally ($P = 0.0095$). No significant

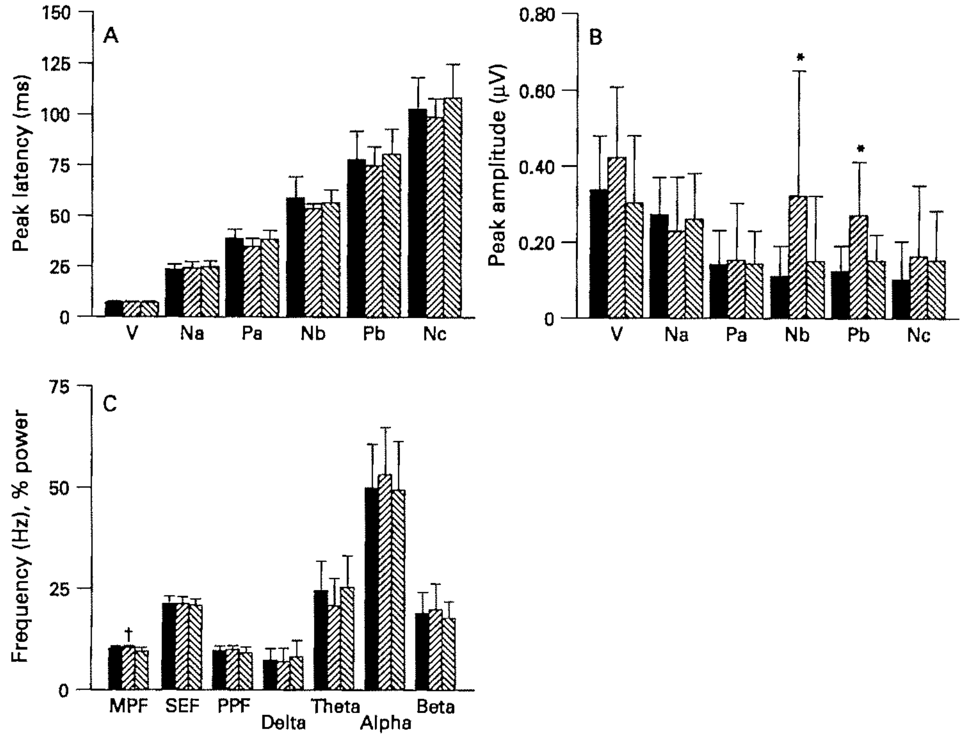


Figure 1 Mean (SD) AEP and EEG features before incision (■) ($n = 32$), between incision and sternotomy (▨) ($n = 6$) and after sternotomy (▧) ($n = 32$), averaged over all patients. (A) AEP latencies; (B) AEP amplitudes; (C) EEG spectral features. †Significant difference between periods (Kruskal–Wallis, $P < 0.05$); *significant difference between pre- and post-incision values (Wilcoxon, $P < 0.025$).

Table 2 Number of patients responsive to incision and sternotomy, and number of these patients for which AEP and EEG data were available during the different recordings periods (before incision/between incision and sternotomy/after sternotomy)

Response	No. of patients	AEP and EEG data available
+ + to incision	3	3/—/3
+ to incision	12	10/3/10
− to incision	24	19/3/19
+ + to sternotomy	4	2/3/4
+ to sternotomy	9	5/1/6
− to sternotomy	26	25/2/22

Table 4 Mean (SD) propofol and alfentanil concentrations for patients responsive, equivocally responsive and unresponsive to incision and sternotomy, and number of patients in each group. *Significant difference in mean propofol concentration between unresponsive and equivocally responsive patients (Wilcoxon, $P = 0.0095$)

Response	Propofol ($\mu g\ ml^{-1}$)	Alfentanil ($ng\ ml^{-1}$)	n
− to incision	3.43 (0.95)*	551 (117)	19
+ to incision	2.50 (0.77)*	514 (158)	10
+ + to incision	3.07 (0.58)	555 (182)	3
− to sternotomy	3.03 (1.04)	537 (129)	22
+ to sternotomy	3.10 (0.94)	503 (99)	6
+ + to sternotomy	3.10 (0.85)	462 (168)	4

difference in concentrations of propofol between patients responsive and unresponsive to incision was found, but this could be because of the small number of patients ($n = 3$) in the responsive group. There was no statistically significant difference in propofol concentrations between patient groups for response to sternotomy.

Table 3 Variables that showed significantly different group means between responsive, equivocally responsive and unresponsive patient groups (Kruskal–Wallis, $P < 0.05$)

Measurement period	Classified by response to incision	Classified by response to sternotomy
Before incision	Nb latency ($P = 0.0100$) Pb latency ($P = 0.0197$) median freq. ($P = 0.0336$) heart rate ($P = 0.0451$) propofol ($P = 0.0258$)	theta power ($P = 0.0237$)
After sternotomy		Pa latency ($P = 0.0080$) Pa amplitude ($P = 0.0035$) Nb amplitude ($P = 0.0158$) Peak power freq. ($P = 0.0072$) Theta power ($P = 0.0105$) Alpha power ($P = 0.0456$)

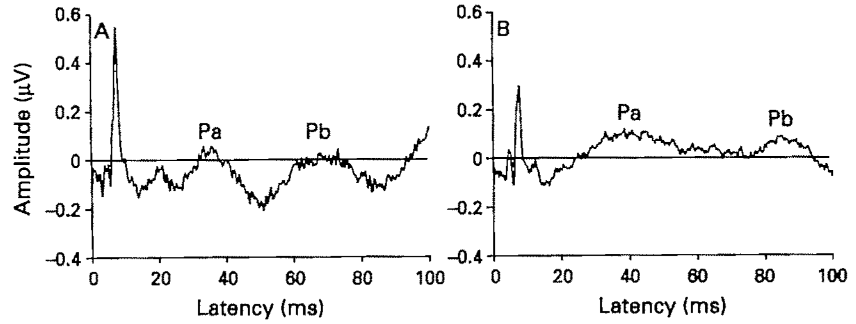


Figure 2 Typical AEP recordings before incision in a patient who was about to respond to incision (A) and in a patient unresponsive to incision (B).

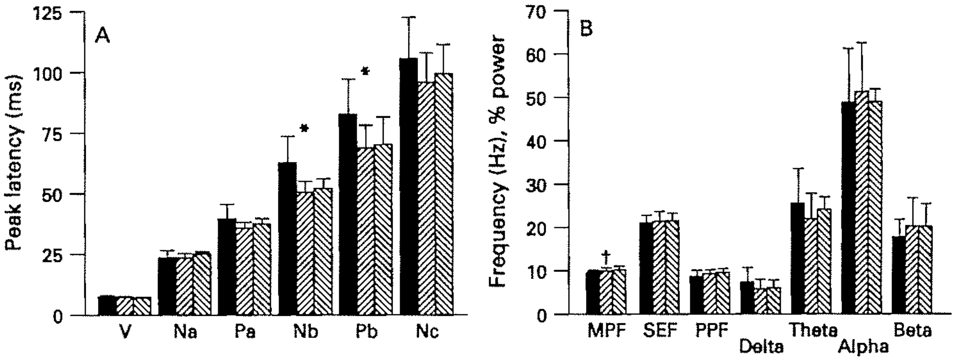


Figure 3 Mean (SD) AEP and EEG features recorded before the first incision, in unresponsive (■), equivocally responsive (▨) and responsive (▧) patients. (A) AEP latencies; (B) EEG spectral features. *Significant difference between group means of patients unresponsive and equivocally responsive to incision (Wilcoxon, $P < 0.025$); †significant overall effect in group means (Kruskal-Wallis, $P < 0.05$).

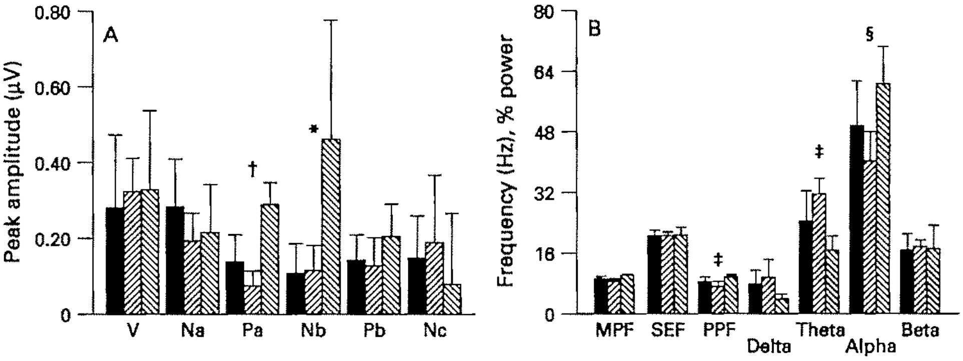


Figure 4 Mean (SD) AEP and EEG features recorded after sternotomy, in unresponsive (■), equivocally responsive (▨) and responsive (▧) patients. (A) AEP amplitudes; (B) EEG spectral features. *Significant difference between group means of patients responsive and unresponsive to sternotomy (Wilcoxon, $P < 0.025$); †significant difference between group means of patients responsive and equivocally responsive, and between group means of patients responsive and unresponsive to sternotomy (Wilcoxon, $P < 0.025$); ‡significant overall effect in group means (Kruskal-Wallis, $P < 0.05$); §significant difference between group means of patients responsive and equivocally responsive to sternotomy.

RESPONSE TO INCISION

Examples of typical AEP recordings for patients responsive and unresponsive to incision are presented in figure 2. Both AEP were recorded before the first incision, in a patient who was about to respond to incision and in a patient unresponsive to incision. In figure 3A, the AEP latencies recorded *before the first incision* are presented for patients responsive, equivocally responsive and unresponsive to the first incision. Latencies of peaks Nb and Pb were significantly longer for patients unresponsive to incision ($P = 0.0100$ and 0.0197, respectively). This effect was statistically significant for the comparison between patients unresponsive and equivocally responsive to incision. The effect was not statistically significant for comparison between patients responsive and unresponsive to incision, but this could be because of the small number of observations ($n = 3$) in the responsive group. In the EEG features recorded before incision presented in figure 3B, there was a statistically significant overall effect ($P = 0.0336$) for the response to incision in median frequency. However, pairwise comparisons revealed no statistically significant differences between any two group means.

Table 5 Performance in terms of sensitivity (Sens.), positive predictive accuracy (Pos. pr.) and total accuracy (Acc.) of different combinations of types of measured variables to predict the occurrence of a haemodynamic response to incision. Chance levels for sensitivity, positive predictive accuracy and total accuracy are 33%

Variable group	Variables selected in discriminant function	Sens. (%)	Pos. pr. (%)	Acc. (%)
Haemodynamic variables	HR, DAP, MAP	69	53	59
Haemodynamic+EEG	HR, median freq., DAP, MAP	62	53	56
Haemodynamic+AEP	Lat. Nb, HR, DAP, MAP, amp. Nc, amp. Na	85	63	72
Haemodynamic+AEP+EEG	Lat. Nb, median freq., HR, DAP, MAP, amp. Na, amp. Nc	85	61	72

RESPONSE TO STERNOTOMY

In figure 4A, the AEP amplitudes recorded *after sternotomy* are presented for patients responsive, equivocally responsive and unresponsive to sternotomy. Amplitudes of peaks Pa and Nb were significantly larger for patients unequivocally responsive to sternotomy ($P = 0.0035$ and 0.0158, respectively), both in comparison with unresponsive and equivocally responsive patients for Pa amplitude. For Nb amplitude only the difference between group means of responsive and unresponsive patients was statistically significant. In figure 4B, EEG spectral features recorded *after sternotomy* are presented for patients responsive, equivocally responsive and unresponsive to sternotomy. The peak power frequency was significantly higher for patients responsive to sternotomy ($P = 0.0072$) compared with equivocally responsive patients. The percentage theta power was significantly lower for patients responsive to sternotomy ($P = 0.0105$) compared with equivocally responsive patients. Before incision, the percentage theta power was also lower in this group ($P = 0.0237$). There was a significant overall effect in percentage alpha power ($P = 0.0456$), but in pairwise comparisons there were no significant differences between group means.

PREDICTING THE RESPONSE TO INCISION

The variables used in the discriminant function and its performance in predicting the responses of individual patients as determined by leave-one-out cross validation are summarized in table 5. Predictions of the best discriminant function using a combination of haemodynamic variables and features from the AEP are summarized in table 6. Predictions of the best discriminant function using a combination of haemodynamic variables and features from both the AEP and EEG are also summarized in table 6. All results were obtained by leave-one-out cross validation. From these results it can be seen that adding features from the EEG to the classifier improved the detection of absence of a response, but also caused overestimation of an equivocal response in one patient. However, overestimation of a response is clinically less relevant than underestimation of a response. Both discriminant functions underestimated an unequivocal response in one of three patients responsive to incision. The presence of an equivocal response was underestimated by both discriminant functions in one of 10 patients equivocally responsive to incision.

Table 6 Predictions of the best discriminant functions using a combination of haemodynamic variables and features from the AEP and a combination of haemodynamic variables and features from both the AEP and EEG. For each combination of actual and predicted response group the total number of observations is shown

Predicted response	0	1	2
Haemodynamic and AEP features			
Actual response			
0	12	7	0
1	1	9	0
2	0	1	2
Haemodynamic, AEP and EEG features			
Actual response			
0	13	6	0
1	1	8	1
2	0	1	2

Discussion

EFFECT OF PAIN ON THE AEP AND EEG

Our first aim was to determine if AEP and EEG features are sensitive to pain stimuli. It was found earlier by Thornton and colleagues [3] that amplitudes of peaks Nb and Pb increased significantly after the start of surgery. This is consistent with our observation that Nb and Pb amplitudes increased significantly after incision, which indicates that AEP amplitudes appear to be sensitive to pain stimuli. Nb and Pb amplitudes did not increase further and even decreased after sternotomy (when averaged over all patients), but this could be because of the increasing drug concentrations. The last setting in our stepped infusion scheme for propofol and alfentanil was reached on average at incision, but in some patients this last setting was reached only after sternotomy. This explanation for a decrease in Nb and Pb amplitudes after sternotomy is supported by the observed increase in AEP latencies, as indicated in figure 1.

A second observation that supports the hypothesis that AEP amplitudes are sensitive to pain stimuli is the increase in AEP amplitudes after sternotomy for the group of patients responsive to sternotomy. One would also expect an increase in AEP amplitudes after incision for patients responsive to incision, but we did not find such an increase. A possible explanation for this is the low number of observations available during the period between incision and sternotomy for responsive patients.

In the EEG features we found a significant effect only in median frequency between the three recording periods, averaged over all patients. This effect was not found in pairwise comparisons between recording periods. Although median and peak power frequency, and percentages of alpha and beta power tended to increase after incision, and percentages of delta and theta power tended to decrease after incision, these changes were not statistically significant. After sternotomy we observed a decrease in characteristic frequencies and percentages of alpha and beta power, and an increase in percentages of delta and theta power, when averaged over all patients. Similar to the effect in AEP latencies and amplitudes after sternotomy, this could have been because of increasing drug concentrations.

When the EEG features were studied for the different response groups, we found an effect on peak power frequency and percentages of theta and alpha power after sternotomy. However, we cannot be sure that this effect was caused entirely by the painful stimulus of sternotomy, because the difference between response groups in percentage theta power was already present before incision.

PREDICTION OF A RESPONSE TO INCISION

Our second aim was to examine if there were differences in AEP and EEG features between responsive and unresponsive patients, before the occurrence of a response. For AEP features this has not been studied previously. For EEG spectral features, it has been shown that these may predict movement in response to incision, and that EEG spectral features are better predictors for movement in response to incision than haemodynamic variables [2, 9]. In this study, we found Nb and Pb latency to be significantly longer for patients who did not show a haemodynamic response to incision. Moreover, there was no difference in arterial pressures between response groups. The only indication for a possible response was an increased heart rate for patients about to respond to incision, but although there was a significant difference in heart rate between patient groups, mean heart rate for responsive patients was not very high (77.0 (SD 12.8) beat min^{-1}). We found an increased median, spectral edge and peak power frequency in patients about to respond to incision, but only median frequency showed a statistically significant overall effect, and the pairwise comparisons between patient groups were not statistically significant. Thus, if we define adequate anaesthesia as absence of a haemodynamic response to incision, AEP seem more suitable to predict inadequate anaesthesia than EEG features and haemodynamic variables measured before incision.

Although we had expected to find a difference in propofol and alfentanil concentrations between responsive and unresponsive patients, we found a statistically significant difference only in propofol concentrations between patient groups for response to incision. The absence of a significant difference in propofol concentrations between unresponsive and responsive patients in the presence of a significant difference between unresponsive and equivocally responsive patients could be because of the small number of observations in the responding group. This may also explain the absence of a significant effect in alfentanil concentrations, because there was a tendency for alfentanil concentrations to be lower for patients responsive to sternotomy.

Finally, we attempted to predict the response to incision for each patient, using haemodynamic variables recorded before incision, and features from the AEP and EEG recorded before incision. We found that the best prediction of a response to incision was obtained by combining haemodynamic variables with features from the AEP. Including features from the EEG decreased slightly the positive predictive accuracy, that is the probability that a predicted response or equivocal response is not an overestimation of the actual response. The discriminant function thus obtained had a total accuracy of 72%. Although this does not seem very high, it should be noted that using only haemodynamic variables in the discriminant function resulted in a total accuracy of only 59%. Total accuracy on chance level would be 33%, because we used three possible response classes.

CHOICE OF A CLINICAL END-POINT

When monitoring the presence or absence of pain during general anaesthesia, possible clinical end-points are movement or haemodynamic responses to noxious stimulation. The latter option, which we chose to use in this study, has the advantage of providing a graded assessment of the presence or absence of pain. Another consideration is that absence of movement is probably associated with lighter levels of anaesthesia than absence of a haemodynamic response. Because during cardiac surgery relatively deep levels of anaesthesia are needed at sternotomy and sternal spread, we considered absence of movement in response to incision less appropriate than absence of a haemodynamic response to indicate adequate anaesthesia. In addition, movement in response to a noxious stimulus is not a reliable indicator of pain when neuromuscular blockers are administered.

ROUTINE MONITORING OF THE AEP AND EEG

The feasibility of routine AEP and EEG monitoring in the operating theatre is questionable at present, as indicated by our inability to reliably obtain an AEP waveform in all patients during all recording periods. This was partly because of short time between incision and sternotomy in several patients and partly because of the use of electrosurgery during the entire period after incision. Although the algorithm developed in our group for detecting and rejecting this type of artefact appeared to be adequate [14], the remaining amount of signal that was undisturbed by artefacts was not always sufficient to produce a reliable AEP waveform. Using EEG amplifiers with higher input impedances may help in alleviating this problem. Another consideration is the amount of time needed to obtain a reliable AEP waveform. When the AEP, EEG, or both, are used for dynamic monitoring of pain responses, they should be easy to obtain, rapidly. Although the EEG can be obtained more rapidly than the AEP, the EEG itself does not seem to be useful for monitoring pain responses, according to our results. The acquisition times used for obtaining an AEP waveform in this study were relatively long (up to 10 min). Because all AEP waveforms were analysed off-line, this recording time was chosen to compensate in advance for the occurrence of artefacts. The method for random presentation of stimuli used in this study may produce an acceptable AEP waveform within 40–60 s in the absence of artefacts [19]. However, if the AEP is to be used routinely, in an environment where the occurrence of artefacts is to be expected, one would need an on-line assessment of the reliability of the obtained AEP waveform.

We conclude that the AEP is more sensitive to pain stimuli than the EEG. Features from the AEP may provide additional information on the adequacy of anaesthesia, although 100% accurate prediction of the presence or absence of a haemodynamic response to incision was not possible using a combination of AEP and haemodynamic variables.

Acknowledgements

This study was supported by grant 90-CA from the Co-operation Center Tilburg and Eindhoven Universities, The Netherlands. Additional grants were received from Janssen Pharmaceuticals, Zeneca Farma and the Scientific Fund of the Catharina Hospital Eindhoven.

References

1. Sebel PS, Rampil I, Cork R, White P, Smith NT, Brull S, Chamoun N. Bispectral analysis for monitoring anesthesia—a multicenter study. *Anesthesiology* 1993; **79**: A178.
2. Kearse LA, Manberg P, Chamoun N, deBros F, Zaslavsky A. Bispectral analysis of the electroencephalogram correlates with patient movement to skin incision during propofol/ nitrous oxide anesthesia. *Anesthesiology* 1994; **81**: 1365–1370.
3. Thornton C, Konieczko KM, Jones JG, Jordan C, Doré CJ, Heneghan CPH. Effect of surgical stimulation on the auditory evoked response. *British Journal of Anaesthesia* 1988; **60**: 372–378.
4. Thornton C, Barrowcliffe MP, Konieczko KM, Ventham P, Doré CJ, Newton DEF, Jones JG. The auditory evoked response as an indicator of awareness. *British Journal of Anaesthesia* 1989; **63**: 113–115.
5. Thornton C. Evoked potentials in anaesthesia. *European Journal of Anaesthesiology* 1991; **8**: 89–107.
6. De Beer NAM, van Hooff JC, Cluitmans PJM, Korsten HHM, Grouls RJE. Correlation of the EEG and AEP with blood levels of propofol and alfentanil. *Anesthesiology* 1994; **80**: A480.
7. Schwender D, Haessler R, Klasing S, Madler C, Pöppel E, Peter K. Mid-latency auditory evoked potentials and circulatory response to loud sounds. *British Journal of Anaesthesia* 1994; **72**: 307–314.
8. Schwender D, Kaiser A, Klasing S, Peter K, Pöppel E. Midlatency auditory evoked potentials and explicit and implicit memory in patients undergoing cardiac surgery. *Anesthesiology* 1994; **80**: 493–501.
9. Dutton RC, Smith WD, Smith NT. Does the EEG predict anesthetic depth better than cardiovascular variables? *Anesthesiology* 1990; **73**: A532.
10. Thornton C. *Assessment of Graded Changes in the Central Nervous System, during General Anaesthesia and Surgery in Man, using the Auditory Evoked Response*, PhD Thesis. London: University of London, 1990.
11. Krausz HI. Identification of nonlinear systems using random impulse train imputs. *Biological Cybernetics* 1975; **19**: 217–230.
12. Cluitmans PJM, Beneken JEW. Non-linear analysis of sensory evoked potentials. In: Nagel JH, Smith WM, eds. *Proceedings of the 13th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. Piscataway: IEEE Press, 1991; **13**: 419–420.
13. Cerutti S, Carrault, Cluitmans PJM, Kinie, Lipping, Nikolaidis, Pitas, Signorini. Non linear algorithms for processing biological signals. *Computer Methods and Programs in Biomedicine* (in press).
14. De Beer NAM, van de Velde M, Cluitmans PJM. Clinical evaluation of a method for automatic detection and removal of artifacts in auditory evoked potential monitoring. *Journal of Clinical Monitoring* 1995; **11**: 381–391.
15. Van de Velde M, Cluitmans PJM. *EEG Analysis for Monitoring of Anaesthetic Depth*. EUT-report 91-E-254, ISBN 90-6144-254-0. Eindhoven: Eindhoven University of Technology, 1991.
16. Schwilden H, Stoeckel H, Schüttler J. Closed-loop feedback control of propofol anaesthesia by quantitative EEG analysis in humans. *British Journal of Anaesthesia* 1989; **62**: 290–296.
17. Vernon J, Bowles S, Sebel PS, Chamoun N. EEG bispectrum predicts movement at incision during isoflurane or propofol anesthesia. *Anesthesiology* 1992; **77**: A502.
18. Michiels M, Hendriks R, Heykants J. Radioimmunoassay of the new opiate analgesics alfentanil and sufentanil. Preliminary pharmacokinetic profile in man. *Journal of Pharmacy and Pharmacology* 1983; **35**: 86–93.
19. Van de Velde M, Cluitmans PJM, Declerck AC. Optimization of stimulation frequency in middle latency auditory evoked potentials in humans. *Technology and Healthcare* 1993; **1**: 340–341.

British Journal of Anaesthesia 1996; **76**: 694–698

Double-blind, randomized trial of cessation of smoking after audiotape suggestion during anaesthesia

P. S. MYLES, M. HENDRATA, Y. LAYHER, N. J. WILLIAMS, J. L. HALL, J. T. MOLONEY AND J. POWELL

Summary

We studied the use of intraoperative tape suggestion to improve the rate of cessation of smoking in 363 smokers who wanted to stop smoking. They were allocated randomly to hear a taped message encouraging them to stop smoking or to a blank tape, played during general anaesthesia. Overall 56 patients (15.4%, 95% confidence interval (CI) 11.7–19.1%) had claimed to have stopped smoking at 2 months and 29 patients (8.0%, 95% CI 5.9–10.1%) were confirmed to have stopped smoking at 6 months. There was no significant difference between the groups at either 2 or 6 months (risk ratios 1.06 and 1.09, respectively, $P = 0.78$). A preoperative: postoperative ratio of a visual analogue scale measuring the patient's motivation to stop smoking was not significantly different (control group 1.13 *vs* message group 1.10, $P = 0.55$). This study does not support the hypothesis that intraoperative tape suggestion can change smoking behaviour. (*Br. J. Anaesth.* 1996; **76**: 694–698)

Key words

Anaesthesia: depth. Memory. Complications, smokers.

Smoking is a major health risk, with almost 20% of all deaths in developed countries attributed to tobacco [1]. There have been some reports of successful smoking cessation interventions during the perioperative period, which relied upon auditory "awareness" during anaesthesia [2–4]. However, these studies can be criticized because of major methodological flaws (either unblinded, or absence of confirmation of cessation of smoking at follow-up). Nevertheless, the nature of the surgery and the postoperative period may allow patients to reassess their smoking behaviour.

Awareness during anaesthesia is a major concern for many patients undergoing surgery [5–8]. Awareness commonly involves meaningful sounds or, more rarely, pain perception. It may be conscious (explicit recall) or subconscious (implicit recall), such that implicit recall may not be detected unless under hypnosis or by assessing non-verbal behaviour [5, 8–11]. Cortical auditory evoked potentials are not abolished during general anaesthesia using inhalation agents, despite adequate depth of anaesthesia for surgery [12, 13]. Thus registration of auditory stimuli may occur during routine general anaesthesia. This phenomenon has been reviewed recently [11, 14]. Despite the harmful effects of (unintentional) awareness, a beneficial (intentional) effect on postoperative recovery has been demonstrated with audiotape suggestion [15–17]. An editorial in the *Lancet* suggested that tape recordings could be used with therapeutic "commercial breaks" [18]. Nevertheless, more recent work is conflicting and whether or not intraoperative tape suggestion can effect postoperative behaviour is still in doubt [19, 20].

In this prospective, randomized, double-blind study, we have investigated if tape suggestion during general anaesthesia could be used to promote cessation of smoking in patients who present for elective surgery.

Patients and methods

Patients undergoing elective or semi-elective surgery were enrolled after Ethics Committee approval and written informed consent (which included the fact that they had an equal chance of receiving a blank or message tape). To be eligible for inclusion in the study, patients had to be current daily cigarette smokers (at least two cigarettes per day for at least 21 of the last 28 days) who were sure they wished to stop smoking at that time. Exclusion criteria were pre-existing major medical disorders (major/active malignancy, AIDS, hepatic, renal, cardiac or respiratory disease), a short life expectancy (less than 12 months), cardiac surgery or where the nature of the surgery excluded the use of headphones, hearing deficit, poor English comprehension, history of psychiatric illness, intellectual disability or alcoholism.

All patients were informed briefly about the normal process of general anaesthesia and the nature of subconscious learning or "awareness". They were informed of the accepted health risks of smoking and advised to give up smoking; no other anti-smoking measures were used.

Patients were allocated randomly from a table of random numbers. The treatment group ("message

---

PAUL S. MYLES, MB, BS, MPH, FRCA(IREL), FANZCA, MELANIE HENDRATA, RN, YASMINE LAYHER, MB, BS, NICKY J. WILLIAMS, MB, BS, BSC, FRCA, JENNIFER L. HALL, MB, BS, FANZCA, JOHN T. MOLONEY, MB, BS, FANZCA, JAMES POWELL, MB, BS, FRCA, Alfred Hospital, Commercial Road, Prahran, Victoria 3181, Australia. Accepted for publication: January 12, 1996.

Correspondence to P.S.M.

group") received the suggestion tape while the control group received the blank tape. Both tapes were indistinguishable and identity was established at completion of the study. The suggestion tape consisted of 3 min of reassurance, explanation and positive encouragement to give up smoking (see appendix). The transcript had been vetted by a clinical psychologist. The tapes were checked for clarity on a regular basis throughout the study and on completion.

After induction of general anaesthesia, the headphones were applied in such a way as to prevent external transmission of sound. The tape was commenced at the first surgical incision and stopped at the end of wound closure while the patient was still anaesthetized. Using a compact portable cassette recorder and headphones (Sony model No. WMFX30), the suggestion tape was played continuously, repeating the 3-min message. Previous testing of this system had excluded external transmission of sound (other than to the patient). Thus theatre personnel and the investigators were blinded to the tape content.

At the preoperative visit, patients were asked to grade their motivation to give up smoking using a 100-mm visual analogue scale (VAS). Details of their smoking history were obtained and the presence of smoking-related diseases noted (ischaemic heart disease, asthma, chronic obstructive airways disease, peptic ulcer). Details of the general anaesthetic were recorded, as was the type and duration of surgery.

After surgery, patients were asked if they had any memory of spoken words during operation and the VAS was repeated. The ratio of the postoperative: preoperative VAS was used as an index of change in motivation to stop smoking. All patients were contacted by telephone (or if uncontactable, by letter) at 2 and 6 months to ascertain their level of smoking.

DEFINITION OF ABSTINENCE

At 2 months, abstinence was defined as patient-reported no cigarette puffs for at least 28 days. At 6 months, patients reporting cessation of smoking were asked to attend hospital for confirmation of their non-smoking status; abstinence was then verified by end-expired carbon monoxide analysis (Bedfont Micro Breathalyser, Southgate, Sydney), defined as carbon monoxide concentration less than 8 ppm.

STATISTICAL ANALYSIS

A preliminary estimate of sample size was based on doubling the expected smoking cessation rate in the treatment group (from 10% to 20%) [3]. With a type I error of 0.05 and a type II error of 0.2, the required total number was calculated at 532 patients (Clinical Trials Design Program V1.0, Biosoft, Cambridge, UK). An unplanned interim analysis was performed after completed follow-up of 240 patients (363 patients enrolled) because of slow recruitment. A smoking cessation rate of 9.6% at 6 months was found. This result supported the conclusion that there was unlikely to be any therapeutic benefit from tape suggestion and the study was therefore stopped [21].

Patient data are presented as proportions, mean (SD) and range. The ratio of postoperative: preoperative VAS for the two groups was compared using the unpaired Student's *t* test (two-tailed). The number of patients who had stopped smoking was analysed using chi-square with Yates' correction. In the outcome analysis, the intention-to-treat principle was applied and patients lost to follow-up were assumed to be still smoking. $P < 0.05$ was considered significant. All statistical analyses were performed using SPSS v4.0 (SPSS Inc, Sydney, Australia).

Results

We enrolled 363 patients in the study, and they averaged 21 cigarettes per day for 19 years. Patient characteristics are shown in table 1; there were no significant differences between the groups. Fourteen patients (seven in each group) were lost to follow-up at 2 months and another 23 patients (10 control group, 13 message group) at 6 months. A total of 56 (15.4%, 95% confidence interval (CI) 11.7–19.1%) patients claimed to have stopped smoking at 2 months and 29 (8.0%, 95% CI 5.9–10.1%) were confirmed to have stopped smoking at 6 months.

Table 1 Patient characteristics in each group (mean (SD) [range] or proportion (%)). * Pack-years = number of years smoked × average number of packets smoked per day

	Control group (*n* = 178)	Message group (*n* = 185)
Age (yr)	37.1 [18–77]	38.0 [18–74]
Sex (M/F) (% male)	119/59 (67%)	119/66 (64%)
No. of cigarettes smoked per day	21.3 (11) [2–60]	20.0 (10) [2–60]
No. of years smoking	18.6 (12) [1–50]	20.1 (13) [1–57]
Pack-years*	21.4 (22) [1–200]	22.1 (19) [1–85]
Smoking-related diseases		
Chronic sinusitis	23 (13%)	16 (8.6%)
Chronic obstructive airways disease	23 (13%)	13 (7%)
Peptic ulcer disease	19 (11%)	23 (12%)
Ischaemic heart disease	4 (2.2%)	6 (3.2%)
Atopic respiratory disease		
Asthma	21 (12%)	25 (14%)
Hay fever	31 (18%)	30 (16%)
Cohabitation with smoker		
Spouse	62 (35%)	64 (35%)
Other	92 (52%)	94 (51%)
Anaesthesia		
Premedication used:	103 (59%)	117 (63%)
(benzodiazepine/opioid/other)	48/25/30	62/27/28
Induction: thiopentone/propofol/other	43/133/2	65/115/5
Maintenance: isoflurane/enflurane/other	123/52/1	121/59/5
Neuromuscular blocker used:	99 (51%)	111 (60%)
(atracurium/vecuronium/other)	59/12/28	67/20/24
Duration of surgery (min)	50 (41) [4–310]	56 (46) [5–275]

Table 2 Change in motivation to stop smoking (VAS) and cessation rates. The cessation rates include those lost to follow-up who were assumed to be still smokers (see text) (mean (SD) or number (%))

	Control group ($n = 178$)	Message group ($n = 185$)	P
VAS ratio (postop:preop.)	1.13 (0.50) ($n = 164$)	1.10 (0.29) ($n = 164$)	0.55
Cessation at 2 months (self-reported)	26 (17.1 %) ($n = 145$)	30 (19.4 %) ($n = 149$)	0.78
Cessation at 6 months (CO-validated)	13 (7.9 %) ($n = 152$)	16 (9.5 %) ($n = 156$)	0.78

Two patients in each group claimed to have heard noises or voices during operation (including one patient in the message group who remembered hearing the tape message before induction of anaesthesia and not afterwards). None of the three other patients could specifically recall a message and none was distressed after operation.

There was no significant difference between the groups in their motivation to stop smoking (VAS) and smoking cessation rates at 2 and 6 months (table 2). Univariate risk ratios for 2 and 6 months were 1.06 (95 % CI 0.81–1.39) and 1.09 (95 % CI 0.77–1.54), respectively.

Discussion

In this study, the largest reported to date, we found no evidence of any benefit in using tape suggestion during anaesthesia to increase smoking cessation after operation or any evidence of effect on patients' motivation to stop smoking. Only 29 patients (8 %) had stopped smoking at 6 months. This is a disappointing result, particularly as this population represents those recovering from a surgical procedure and expected to be more likely to give up smoking. However, it is consistent with other reported rates of spontaneous cessation of smoking [22].

Interestingly, two patients from each group reported auditory awareness during their anaesthetic, although all without explicit memory of surgery or undue anxiety. Explicit recall was therefore very uncommon (1.1 %). It could be argued that because all patients were wearing ear-plugs and that there was no significant difference between the message and control groups, there may not have been specific auditory awareness and such memory may have been non-specific dreaming [11]. It should be appreciated that we did not investigate this issue comprehensively, which would require specialized follow-up, including assessment of non-verbal behaviour and possibly hypnosis [8, 11]. Previous authors have suggested that the content of the tape message is crucial and in this study the tape transcript had been vetted by an experienced clinical psychologist. The identity of the person delivering the message is also considered important, but personalizing such a message is unwieldy for widespread use and previous studies have supported the use of a single speaker.

Can intraoperative tape suggestion change behaviour? Liu, Standen and Aikenhead [19] set out to reproduce a previous study by Evans and Richardson [16] who had demonstrated improved postoperative recovery with tape suggestion. They could find no effect of positive tape suggestion during anaesthesia and concluded that the weight of evidence in favour of a change in postoperative behaviour was questionable, and that a larger study was required to definitively answer this question. Other recent studies have shown similar negative results [23–25]. Nevertheless, evidence for implicit memory formation appears to be stronger, with a clear (negative) relationship between increasing depth of anaesthesia (as measured by auditory evoked potentials) and perhaps type of anaesthetic agent, with implicit recall [13, 26]. It is therefore feasible that the anaesthetic techniques used in this study may have impeded implicit memory formation and therefore the ability to influence postoperative behaviour. But this raises a problem central to intraoperative tape suggestion: if an anaesthetic technique is tailored to enhance implicit memory formation, the risk of inadvertent awareness is probably increased. The only solution is to identify anaesthetic agents that allow implicit memory formation, yet ensure absence of recall; current evidence suggests this would be unlikely.

Successful cessation of smoking after perioperative suggestion was first reported by Aldrete in 1987 [2], after he studied 25 patients and arbitrarily allocated them to one of three groups according to motivation to stop smoking. He then used repeat verbal suggestions before, during and after operation (i.e. patients were sometimes awake). He found that seven of the highly motivated group ($n = 9$) had stopped smoking at 12 months, compared with only two of the moderately motivated group ($n = 7$) and one of the "control" group ($n = 9$). Although encouraging, this study was flawed in its design (small sample, unblinded, not randomized) and interpretation. Similar studies have been published since which support an effect of tape suggestion on smoking cessation [3, 4], but they are also flawed. In particular, cessation of smoking was defined by self-reporting and was not confirmed biochemically [27]. Interestingly, Hughes and colleagues [4] found a significant difference in cessation rates at 1 month, but none of the control group reported cessation of smoking compared with eight in the intervention group ($n = 50$). This conflicts with most smoking cessation studies, which demonstrate a background cessation rate in the control group of about 15–20 % during the early follow-up period (i.e. similar to the intervention group). This supports Millar's explanation of other conflicting studies [20].

Smoking has well-recognized health risks which are often accentuated in the perioperative period [1, 22, 28–32]. The pathophysiological changes that are detrimental to anaesthesia and surgery include increased carboxyhaemoglobin concentrations (and therefore decreased oxygen-carrying capacity), tachycardia and hypertension, increased respiratory secretions and irritability of upper airway reflexes, and decreased immunological function (neutrophil activity, immunoglobulin concentrations, natural killer cells) [28]. Adverse effects have also been documented during the recovery phases, with impaired wound healing [30], respiratory complications [33, 34] and increased length of stay in the recovery room [31]. It is clear that smoking is an important risk factor for anaesthesia and surgery. The original condition leading to hospitalization and surgery may also be associated with smoking [35]. Although the published literature concerning perioperative cessation of smoking is sparse, it appears that patients do not heed such advice given before operation [36]. The time spent in hospital, particularly during recovery after surgery, offers a unique opportunity for medical practitioners to encourage smoking cessation; anaesthetists can share in this role.

Appendix

TRANSCRIPT OF TAPE SUGGESTION

Your operation is going very well.
It is common to hear talking during your operation. There is no need to worry. The doctors are very happy. Your operation is going well.
You would like to give up smoking.
It is a very good idea that you give up smoking.
You will not miss smoking at all.
Smoking is a very dirty and unhealthy habit.
You will succeed in becoming a non-smoker because this is a decision that you have made, because this is something that you choose.
You will experience feelings of pride, and others will notice your change.
You have outgrown your need to smoke to be part of a group. You are confident and assured of your ability to be smoke-free anywhere.
You will find that when you are in a car, or with friends who smoke, you will feel good in knowing that you are a non-smoker.
When offered a cigarette, you will feel proud to say no; you will refuse to smoke.
When you give up smoking you will feel healthier.
When you give up smoking you will live longer.
You will feel proud to be a non-smoker.

Acknowledgements

We thank Dr Steve Gourlay for his constructive advice and Ms Doris Brett, clinical psychologist, for advice on the audiotape transcript. The following also assisted in the study: Drs C. Hawkins, O. Page, J. Monagle, A. Richards, P. Girdlestone, H. Madder, A. Buettner and others. Research funds were provided by the Alfred Hospital Whole Time Medical Specialist's Private Practice Fund.

References

1. Peto R, Lopez AD, Boreham J, Thun M, Heath C. Mortality from tobacco in developed countries: indirect estimation from national vital statistics. *Lancet* 1992; **339**: 1268–1278.
2. Aldrete JA. Cessation of cigarette smoking by suggestion in the perianesthetic period. *Anesthesiology Reviews* 1987; **14**: 22–24.
3. Myles P. Cessation of smoking following tape suggestion under anaesthesia. *Anaesthesia and Intensive Care* 1992; **20**: 540–541.
4. Hughes JA, Sanders LD, Dunne JA, Tarpey J, Vickers MD. Reducing smoking. The effect of suggestion during general anaesthesia on postoperative smoking habits. *Anaesthesia* 1994; **49**: 126–128.
5. Levinson BW. States of awareness during general anaesthesia. *British Journal of Anaesthesia* 1965; **37**: 544–546.
6. Scott DL. Awareness during general anaesthesia. *Canadian Anaesthetists Society Journal* 1972; **19**: 173–183.
7. Blacher RS. On awakening paralysed during surgery. *Journal of the American Medical Association* 1975; **234**: 67–68.
8. Howard JF. Incidents of auditory perception during anaesthesia with traumatic sequelae. *Medical Journal of Australia* 1987; **146**: 44–46.
9. Goldmann L, Shah MV, Hebden MW. Memory of cardiac anaesthesia. Psychological sequelae in cardiac patients of intra-operative suggestion and operating room conversation. *Anaesthesia* 1987; **42**: 596–603.
10. Bennett HL, Davis HS, Giannini JA. Non-verbal response to intraoperative conversation. *British Journal of Anaesthesia* 1985; **57**: 174–179.
11. Goldmann L. Information-processing under general anaesthesia: a review. *Journal of the Royal Society of Medicine* 1988; **81**: 224–227.
12. Thornton C, Catley DM, Jordan C, Lehane JR, Royston D, Jones JG. Enflurane anaesthesia causes graded changes in the brainstem early cortical auditory evoked response in man. *British Journal of Anaesthesia* 1983; **55**: 479–485.
13. Munglani R, Andrade J, Sapsford DJ, Baddeley A, Jones JG. A measure of consciousness and memory during isoflurane administration: the coherent frequency. *British Journal of Anaesthesia* 1993; **71**: 633–641.
14. Ghoneim MM, Block RI. Learning and consciousness during general anesthesia. *Anesthesiology* 1992; **76**: 279–305.
15. Bonke B, Schmitz PIM, Verhage F, Zwaveling A. Clinical study of so-called unconscious perception during general anaesthesia. *British Journal of Anaesthesia* 1986; **58**: 957–964.
16. Evans C, Richardson PH. Improved recovery and reduced postoperative stay after therapeutic suggestions during general anaesthesia. *Lancet* 1988; **ii**: 491–493.
17. McLintock TTC, Aitken H, Downie CFA, Kenny GNC. Postoperative analgesic requirements in patients exposed to positive intraoperative suggestions. *British Medical Journal* 1990; **30**: 788–790.
18. Editorial. Advertising during anaesthesia? *Lancet* 1986; **ii**: 1019–1020.
19. Liu WHD, Standen PJ, Aitkenhead AR. Therapeutic suggestions during general anaesthesia in patients undergoing hysterectomy. *British Journal of Anaesthesia* 1992; **68**: 277–281.
20. Millar K. Efficacy of therapeutic suggestions presented during anaesthesia: re-analysis of conflicting results. *British Journal of Anaesthesia* 1993; **71**: 597–601.
21. Pocock SJ. When to stop a clinical trial. *British Medical Journal* 1992; **305**: 235–240.
22. Richmond RL, Webster IW. A smoking cessation programme for use in general practice. *Medical Journal of Australia* 1985; **142**: 190–194.
23. Dwyer R, Bennett HL, Eger EI, Peterson N. Isoflurane anesthesia prevents unconscious learning. *Anesthesia and Analgesia* 1992; **75**: 107–112.
24. Jelicic M, Asbury AJ, Millar K, Bonke B. Implicit learning during enflurane anaesthesia in spontaneously breathing patients? *Anaesthesia* 1993; **48**: 766–768.
25. Parker CJR, Oates JDL, Boyd AH, Thomas SD. Memory for auditory material presented during anaesthesia. *British Journal of Anaesthesia* 1994; **72**: 181–184.
26. Schwender D, Kaiser A, Klasing S, Peter K, Poppel E. Midlatency auditory evoked potentials and implicit memory in patients undergoing cardiac surgery. *Anesthesiology* 1994; **80**: 495–501.
27. Myles PS. Smoking reduction and tape suggestion. *Anaesthesia* 1994; **49**: 917–918.
28. Pearce AC, Jones RM. Smoking and anesthesia: preoperative abstinence and perioperative morbidity. *Anesthesiology* 1984; **61**: 576–584.
29. Jones RM, Rosen M, Seymour L. Smoking and anaesthesia. *Anaesthesia* 1987; **42**: 1–2.
30. Silverstein P. Smoking and wound healing. *American Journal of Medicine* 1992; **93**: 22S–24S.
31. Handlin DS, Baker T. The effects of smoking on postoperative recovery. *American Journal of Medicine* 1992; **93**: 32S–37S.
32. Friedman GD, Petitti DB, Bawol RD, Siegelaub AB. Mortality in cigarette smokers and quitters. *New England Journal of Medicine* 1981; **304**: 1407–1410.
33. Forrest JB, Rehder K, Cahalan MK, Goldsmith CH.

Multicenter study of general anesthesia III. Predictors of severe perioperative adverse outcomes. *Anesthesiology* 1992; **76**: 3–15.

34. Duncan PG, Cohen MM, Tweed WA, Biehl D, Pope WDB, Merchant RN, De Boer D. The Canadian four-centre study of anaesthetic outcome: III. Are anaesthetic complications predictable in day surgical practice? *Canadian Journal of Anaesthesia* 1992; **39**: 440–448.
35. D'Arcy C, Holman J, Shean RE. Premature adult mortality and short-stay hospitalization in Western Australia attributable to the smoking of tobacco, 1979–1983. *Medical Journal of Australia* 1986; **145**: 7–11.
36. Munday IT, Desai PM, Marshall CA, Jones RM, Phillips M-L, Rosen M. The effectiveness of pre-operative advice to stop smoking: a prospective controlled trial. *Anaesthesia* 1993; **48**: 816–818.

British Journal of Anaesthesia 1996; **76**: 699–701

Recall during intermittent propofol anaesthesia

O. NORDSTRÖM AND R. SANDIN

Summary

We discontinued temporarily an infusion of propofol for surgical reasons in 20 patients undergoing incontinence surgery. The patients, who had not received neuromuscular blockers, were allowed to regain consciousness to a level enabling them to cough on command, open their eyes, and identify and verbally confirm a randomly assigned digit shown on paper. Thereafter, 5–14 min after discontinuation of the propofol infusion, anaesthesia was reinstituted. Memory of the request to cough, a standard conversation and the digit shown was tested 1 h after anaesthesia and on the following day. Only 35% of patients were able to recall one or more of the stimuli presented during wakefulness or were even able to recall having been "awake", and there were very few differences in memory on the day after surgery compared with 1 h after anaesthesia. In comparison with corresponding stimuli given before anaesthesia, memory of material learned during wakefulness was significantly impaired ($P < 0.0001$). Thus patients temporarily capable of cognitive action during propofol anaesthesia may have no subsequent explicit recall of intraoperative events. (*Br. J. Anaesth.* 1996; **76**: 699–701)

Key words

Anaesthetics i.v., propofol. Complications, awareness. Memory. Anaesthesia, depth.

Drug-induced amnesia for events during anaesthesia is often considered beneficial as it is a common belief that post-traumatic neurosis caused by intraoperative cognition during general anaesthesia is more likely after awareness than where there is no explicit recall. However, this assumption is speculative as there are no data, not only on the incidence of significant cognitive capacity during general anaesthesia, but also on the incidence of awareness and subsequent post-traumatic disorders.

In a case report, Ruprecht described a woman who opened and closed her eyes on command during propofol anaesthesia but she had no subsequent recall [1]. Purposeful movements identified by the isolated forearm technique were found in 72% of patients given midazolam and alfentanil, despite the fact that no subsequent recall was evident [2]. Memory impairment for material learned during steady-state propofol infusion in subhypnotic doses has been described previously [3–6]. In the present study, we investigated amnesia for visual and auditory material presented during a period of wakefulness which was preceded, and also followed, by what seemed to be clinically adequate anaesthesia, thus simulating the sequence of events evident in the 14 published cases of awareness during propofol anaesthesia [7–10].

Patients and methods

The study was approved by the Ethics Committee of the University Hospital, Linköping, Sweden. After obtaining informed consent, we studied 20 female patients, ASA I–II, undergoing intra-vaginal sling operation [11]. Median age was 62 (range 49–85) yr, weight 65 (SD 3) kg and height 162 (6) cm.

Preoperative information included the fact that the patients were to be "awakened" during surgery and requested to cough, and also that after anaesthesia they would be questioned about possible memories. No other information on the nature of memory testing was given. Immediately before anaesthesia, the unpremedicated patients were addressed in a standard way and were shown a randomly assigned digit, 0–9 (128 pt Courier font, black on white background). Patients were requested to confirm verbally the digit. Anaesthesia was induced by i.v. infusion of propofol 0.5 mg kg^{-1}, followed by incremental doses of 20 mg every 20 s until loss of response to verbal command and loss of the eyelid reflex. The propofol infusion was continued at 0.17 mg kg^{-1} h^{-1} and subsequently adjusted to clinical needs. Prilocaine 2.5 mg ml^{-1} (100 ml) with adrenaline 2.5 μg ml^{-1} was infiltrated under the symphysis, and 20 ml of bupivacaine 2.5 mg ml^{-1} with adrenaline 2.5 μg ml^{-1} was used for infiltration of the skin over the symphysis. Oxygen 3 litre min^{-1} was administered via nasal cannulae.

In this type of surgery, suspension of the urethra is examined to prevent leakage during coughing but allow voluntary passing of urine. Thus it is necessary for the patient to cough on command. When the first part of surgery was completed (phase 1), the infusion of propofol was discontinued and the bladder was filled with approximately 300 ml of saline. The patient's name, followed by a request to open the eyes was repeated until this was obeyed. Thereafter, the patient was encouraged to cough. After sufficient coughing for evaluation of surgery, the patient was presented with a second randomly assigned digit,

---

O. NORDSTRÖM, MD, R. SANDIN, MD, PHD, Department of Anaesthesia, Länssjukhuset, S-391 85 Kalmar, Sweden. Accepted for publication: December 22, 1995.

0–9 (not the same as that shown before anaesthesia) and asked to confirm verbally the actual digit. Anaesthesia was again induced and surgery was completed (phase 2).

One hour after surgery patients were asked if they remembered anything immediately before anaesthesia. If this answer did not include the digit shown and the standard conversation, specific questions were asked ("did I show you anything?", "do you remember what I said?"). Thereafter patients were asked if they remembered anything during surgery. If this answer did not include the digit shown, coughing and the standard conversation, specific questions were asked ("did I show you anything?", "did I ask you to do anything?", and—in the event of negative answers—"do you remember having been awake during operation?"). Thereafter patients were asked about dreams during surgery. This questioning was repeated the morning after surgery (approximately 24 h). If at this time patients were unable to recall the stimulus presented, they were given the correct answers and asked if they now could remember.

Until the first memory evaluation 1 h after anaesthesia, no caffeine or drugs other than propofol and local anaesthetics were used on the day of surgery, and only mild non-opioid analgesics were required thereafter.

The incidence of memories for stimuli presented before and during anaesthesia was compared using the Wilcoxon signed rank test. Comparison of doses of propofol and duration of the different phases of anaesthesia in patients who recalled something compared with those who did not was performed by the Mann–Whitney *U* test. $P < 0.05$ was considered significant.

Results

No patient had explicit recall of intraoperative events during propofol infusion. In the period of intraoperative wakefulness, one patient (No 10; table 1) reported having had a bad dream. No other patient reported dreaming.

One hour after surgery, all 20 patients remembered the digit shown before anaesthesia and only one patient could not remember the standard conversation before induction. Seven patients remembered something from the period of wakefulness (table 1). The day after surgery, patient No. 11 had forgotten about the coughing, and the patient who 1 h after anaesthesia could not remember the standard conversation before induction now recalled this. Otherwise, memory testing on the day after surgery was identical to that 1 h after anaesthesia. The reductions in memory for the standard conversation and the digit shown during the period of wakefulness were both significant compared with corresponding types of memory before anaesthesia ($P < 0.0001$). Patients, who during the interview on the day after surgery were unable to remember any of the presented stimuli, were given the correct answers. This did not lead to recall in any patient.

Table 1 Distribution of memory in seven patients who, 1 h after anaesthesia, remembered something from the period of wakefulness

Patient No.	Conversation	Coughing	Digit
5			+
8		+	
10	+		+
11		+	
13			+
19	+	+	+
20			+

Table 2 Doses of propofol for induction, phase 1 (before temporarily discontinuing propofol infusion) and phase 2 (after temporarily discontinuing propofol infusion). Elapsed time from discontinuing the propofol infusion to coughing and verbal confirmation of the digit are shown

	Mean (SD)	Median	Range
Induction dose (mg kg^{-1})	2.3 (0.8)		
Duration phase 1 (min)	40 (17)		
Mean dose phase 1 (mg kg^{-1} min^{-1})	0.21 (0.07)		
Time to coughing (min)		3	0–10
Time to confirming digit (min)		6	2–12
Time to induction 2 (min)		8	5–14
Duration phase 2 (min)	23 (9)		
Mean dose phase 2 (mg kg^{-1} min^{-1})	0.22 (0.02)		

The duration of phase 1, duration of discontinued infusion of anaesthetic (time to induction 2), duration of phase 2, administered doses of propofol and elapsed time from discontinuing the propofol infusion to coughing and verbal confirmation of the digit shown are given in table 2. There were no significant differences between patients with explicit recall and those who could not remember any intraoperative event.

Discussion

In the present study, patients were allowed to regain consciousness and perform cognitive actions during propofol anaesthesia. However, after anaesthesia, 65% of patients were unable to remember having been "awake" and significantly better memory was found for both verbal and visual stimuli when learning occurred immediately before induction compared with that in the period when the propofol fusion was discontinued temporarily.

The true incidence of explicit recall of events experienced during general anaesthesia is not known. Limited data indicate an incidence of approximately 2 per 1000 if neuromuscular block is used in both total i.v. [10, Nordström, unpublished observations] and other types of general anaesthesia [12]. However, most anaesthetics are associated with at least some anterograde amnesia [13] and the question may arise as to whether patients may suffer from intraoperative wakefulness despite a lack of explicit recall. Indeed, as assessed by the isolated forearm technique, Russell found that midazolam and alfentanil, in addition to neuromuscular block, were associated with purposeful movements on command without any subsequent explicit recall in 72% of patients [2]. In a case report by Rupreht, a similar situation was found during i.v. anaesthesia based on propofol (opening and closing of the eyes on command without recall) [1]. Amnesia for visual and verbal stimuli presented during propofol infusion has been described previously. In some of these studies, the amnesic effect for visual stimuli was minimal unless patients were sedated profoundly [3, 5, 6], while Veselis and colleagues found a significant amnesic effect for verbal material that was statistically independent of the degree of sedation [4]. In that study, using subhypnotic doses of propofol, partial amnesia for complex visual stimuli was also evident.

However, in previous studies, amnesia has been tested for material presented during maximal drug concentration, where the period of drug infusion has been preceded, and also followed, by no drug administration. This may not be entirely similar to the situation in which most published cases of awareness during propofol anaesthesia have occurred. In these cases, the induction dose was sufficient for rendering the patient unconscious while subsequent administration of anaesthetics some time thereafter was insufficient to meet the patient's needs because of misjudgement or technical errors. Therefore, we investigated post-anaesthesia recall for visual and auditory stimuli presented to patients capable of cognitive action (coughing and opening eyes on command, verbal confirmation of a digit shown) where the period of wakefulness (in order to mimic awareness during maintenance of "anaesthesia") was preceded, and also followed, by a level of anaesthesia where no response to verbal commands or eyelid reflexes were evident. The present study is not entirely similar to clinical cases of awareness as our patients were not distressed by the experience of being aware and paralysed. However, if distress is important for promoting learning, it should be noted that the rapid filling of the bladder during wakefulness seemed to be invariably unpleasant.

Thus patients may be awake and capable of cognitive action during propofol anaesthesia despite a lack of explicit recall. The fact that 65 % of patients were unable to remember anything during surgery can be interpreted in different ways. First, it is a common belief that prevention of explicit recall in case of cognition and distress during general anaesthesia reduces significantly the risk of post-traumatic neurosis. Thus the amnesic action should be beneficial for the patient's mental outcome. On the other hand, it is unacceptable that patients may suffer during neuromuscular block anaesthesia while being incapable of conveying this.

References

1. Rupreht J. Awareness with amnesia during total intravenous anaesthesia with propofol. *Anaesthesia* 1989; **44**: 1005.
2. Russell IF. Midazolam–alfentanil: an anaesthetic? An investigation using the isolated forearm technique. *British Journal of Anaesthesia* 1993; **70**: 42–46.
3. Smith I, Monk TG, White PF, Ding Y. Propofol infusion during regional anesthesia: sedative, amnestic, and anxiolytic properties. *Anesthesia and Analagesia* 1994; **79**: 313–319.
4. Veselis RA, Reinsel RA, Wronski M, Marino P, Tong WP, Bedford RF. EEG and memory effects of low-dose infusions of propofol. *British Journal of Anaesthesia* 1992; **69**: 246–254.
5. White PF, Negus JB. Sedative infusions during local and regional anaesthesia: a comparison of midazolam and propofol. *Journal of Clinical Anesthesia* 1991; **3**: 32–39.
6. Patterson KW, Casey PB, Murray JP, O'Boyle CA, Cunningham AJ. Propofol sedation for outpatient upper gastrointestinal endoscopy: comparison with midazolam. *British Journal of Anaesthesia* 1991; **67**: 108–111.
7. Schäfer HG, Marsch SCU. Wach in totaler intravenöser anaesthesie (Awareness under total intravenous anaesthesia). *Anaesthesist* 1990; **39**: 617–618.
8. Kelly JS, Roy RC. Intraoperative awareness with propofol–oxygen total intravenous anesthesia for microlaryngeal surgery. *Anesthesiology* 1992; **77**: 207–208.
9. Moerman MD, Bonke B, Oosting J. Awareness and recall during general anaesthesia. *Anesthesiology* 1993; **79**: 454–464.
10. Sandin R, Nordström O. Awareness during total i.v. anaesthesia. *British Journal of Anaesthesia* 1993; **71**: 782–787.
11. Papa Petros PE, Ulmsten U. The development of the intravaginal slingplasty procedure: IVS II. *Scandinavian Journal of Urology and Nephrology* 1993; **S 153**: 61–67.
12. Liu WHD, Thorp TAS, Graham SG, Aitkenhead AR. Incidence of awareness with recall during general anaesthesia. *Anaesthesia* 1991; **46**: 435–437.
13. Ghoneim MM, Block RI. Learning and consciousness during general anesthesia. *Anesthesiology* 1992; **76**: 279–305.

British Journal of Anaesthesia 1996; **76**: 702–706

LABORATORY INVESTIGATIONS

Volatile anaesthetics antagonize nitrous oxide and morphine-induced analgesia in the rat

T. GOTO, J. J. A. MAROTA AND G. CROSBY

Summary

We reported previously that nitrous oxide induces pre-emptive analgesia that is partially antagonized by naloxone and totally antagonized by halothane. The aims of this study were to determine if halothane and isoflurane are similar in this respect and to examine if volatile anaesthetics antagonize the analgesic effect of exogenous opioids. We found that 75% nitrous oxide prolonged tail-flick latency by 37% and this analgesia was dose-dependently inhibited by halothane and, less effectively, by isoflurane. In contrast, morphine 1.25 mg kg^{-1} i.v. also prolonged tail-flick latency by 35% but, unlike nitrous oxide-induced analgesia, this effect was attenuated only by high doses of halothane and was unaffected by isoflurane. Neither halothane nor isoflurane alone altered the tail-flick response. We conclude that both halothane and isoflurane dose-dependently antagonized nitrous oxide analgesia but antagonized morphine-induced analgesia to a lesser extent. (*Br. J. Anaesth.* 1996; **76**: 702–706)

Key words

Anaesthetics gases, nitrous oxide. Anaesthetics volatile, halothane. Anaesthetics volatile, isoflurane. Analgesics opioid, morphine. Interactions (drugs). Rat.

The analgesic actions of anaesthetic agents have been studied extensively over the past several years, but interactions between drugs have not been well characterized. We reported previously that 75% nitrous oxide produces pre-emptive analgesia in the rat formalin test which is antagonized partially by naloxone and completely abolished by 0.5 MAC of halothane [1]. Another study using a similar model demonstrated that isoflurane produced modest antinociception whereas the combination of 1% isoflurane and 70% nitrous oxide did not [2], suggesting that nitrous oxide-induced pre-emptive analgesia may also be attenuated by isoflurane.

Based on these data and evidence that nitrous oxide analgesia is mediated at least in part by the endogenous opioid system [1, 3], it follows that these volatile anaesthetics might also antagonize analgesia produced by an exogenous opioid analgesic. In this study we tested this hypothesis by examining and comparing the influence of halothane and isoflurane on antinociception produced by nitrous oxide or morphine. The tail-flick test was chosen to assess analgesia because, as a spinal reflex [4], the tail-flick response is highly resistant to the hypnotic–sedative effects of anaesthetics [5].

Materials and methods

ANIMAL PREPARATIONS

Studies were performed with the approval of the Institutional Subcommittee on Research Animal Care in 81 male Sprague–Dawley rats (Harlan Sprague Dawley, Indianapolis, IN, USA) weighing 300–325 g. Rats were maintained in a 12-h light–dark cycle (lights on at 07:00) and allowed free access to food and water. Animals assigned to receive morphine had an indwelling i.v. catheter inserted before the experiments. For this purpose, rats were anaesthetized with 1% halothane in oxygen and placed in the supine position. After local infiltration with 0.25% bupivacaine 0.2 ml, the skin was incised in the supraclavicular area, 2–3 mm lateral to the midline. The right external jugular vein was exposed and cannulated with a sterile catheter (PE-50 tubing, Clay Adams, Parsippany, NJ, USA) filled with normal saline containing heparin 100 u. ml^{-1}. The catheter was tunnelled subcutaneously and exteriorized to the interscapular area in the back. After operation rats were housed in individual cages and allowed to recover for at least 48 h before they were used for the experiments. To control for known diurnal fluctuations in responsiveness to nociceptive stimuli [6], experiments were performed between the hours of 10:00 and 22:00 in random order.

TAIL-FLICK TEST

Rats were allocated to one of 17 anaesthetic groups as follows: (1) 75% nitrous oxide ($n = 14$); (2) 0.5 MAC of halothane (0.9% inspired concentration; $n = 5$) (3) 0.5 MAC of isoflurane (1.1%; $n = 6$); (4) 100% oxygen without anaesthetic ($n = 5$); (5–7) 75% nitrous oxide with 0.1, 0.2 or 0.5 MAC of halothane ($n = 6$, 4, 5 per group, respectively);

TAKAHISA GOTO*, MD, JOHN J. A. MAROTA, PHD, MD, GREGORY CROSBY†, MD, Anesthesia Services, Massachusetts General Hospital and Department of Anaesthesia, Harvard Medical School, Boston, MA 02114, USA. Accepted for publication: December 13, 1995.

*Present address; Department of Anaesthesia, Teikyo University Ichihara Hospital, 3426-3 Anesaki, Ichihara, Chiba 299-01 Japan.

†Address for correspondence: Department of Anesthesiology, University of Wisconsin, B6/319 Clinical Sciences Center, 600 Highland Avenue, Madison, Wisconsin 53747, USA.

(8–10) 75 % nitrous oxide with 0.1, 0.2 or 0.5 MAC of isoflurane ($n = 6$ per group); (11) morphine 1.25 mg kg^{-1} i.v.; (12–14) morphine 1.25 mg kg^{-1} i.v. with 0.2, 0.5 or 0.7 MAC of halothane; (15–17) morphine 1.25 mg kg^{-1} with 0.2, 0.5 or 0.7 MAC of isoflurane ($n = 5$ per group). The inspired concentrations of halothane and isoflurane were calculated on the basis of reported MAC values in the rat of 0.95–1.11 % for halothane [7–9] and 1.38–1.58 % for isoflurane [7–9], and an estimated ratio of end-tidal to inspired concentration of halothane and isoflurane of 0.5–0.6 and 0.7–0.8, respectively, in spontaneously breathing rats after 20 min [7]. The dose of morphine (1.25 mg kg^{-1} i.v.) was chosen because in preliminary experiments it provided the same degree of analgesia as 75 % nitrous oxide.

Anaesthesia was induced by placing the animals in a plexiglass box prefilled and flushed continuously with 3 litre min^{-1} of the anaesthetic in oxygen. Oxygen 100 % was given to animals that received morphine alone. The concentrations of nitrous oxide (Ohmeda 5200 CO_2 analyzer, Madison, WI, USA), halothane, isoflurane (Datex 222 anesthetic agent analyzer, Puritan Bennett, Tewksbury, MA, USA) and oxygen (Ohmeda 5100 oxygen analyzer), and the temperature inside the box were measured continuously. Animals were left undisturbed for 20 min so that they would reach a steady state of anaesthesia. They were then removed briefly from the box (< 30 s) and the tail-flick test was performed. Immediately after one measurement was made, animals were returned to the box and maintained under anaesthesia for another 3 min. Then the tail-flick test was repeated and these two measurements were averaged to yield the tail-flick latency (TFL) during anaesthesia. In addition, the control tail-flick response for each rat was determined by averaging duplicate measurements made in the pre-anaesthetic awake state.

The tail-flick test was performed by placing the tail of each rat over a slit 1.5 cm from a 150-W focused projector bulb. The end-point of the test was removal of the tail; a cut-off time of 6 s was imposed to avoid permanent tissue damage. The pre-anaesthetic TFL was typically in the range 1.5–1.8 s. Results of the test are expressed as maximum percentage effect (MPE) according to the formula:

$$\text{MPE} = \frac{(\text{TFL during anaesthesia}) - (\text{pre-anaesthetic TFL})}{(\text{cut-off time}) - (\text{pre-anaesthetic TFL})} \times 100(\%)$$

For this part of the study, each animal was used twice with at least a 5-day interval between the first and second experiments.

In order to determine the effect of the anaesthetic regimens on physiological variables such as tail skin temperature, Pa_{CO_2} and arterial pressure that can affect tail-flick latency [10–12], additional rats were prepared with femoral artery and vein catheters during approximately 15 min of 1 % halothane–75 % nitrous oxide anaesthesia. Rats were then partially immobilized with a pelvic plaster cast and allowed at least 3 h to recover from surgery and anaesthesia. Rats subsequently received one of the following anaesthetic regimens: (1) 75 % nitrous oxide ($n = 8$); (2, 3) 75 % nitrous oxide with 0.5 MAC of halothane or isoflurane ($n = 4$ per group); (4) morphine 1.25 mg kg^{-1} i.v. ($n = 8$); (5, 6) morphine with 0.5 MAC of halothane or isoflurane ($n = 4$ per group). At the end of 20 min of anaesthesia, tail temperature, mean arterial pressure (MAP) and arterial blood-gas tensions were measured. For measurement of tail temperature, a hypodermic needle temperature probe (Model HYP2; Omega, Stamford, CT, USA) was inserted 2 mm into the skin between the middle and distal thirds of the ventral aspect of the tail (i.e. the portion of the tail where thermal stimuli were applied during the tail-flick test) and temperature recorded by a microprocessor thermometer (Model HH21: Omega, Stamford, CT, USA). For this part of the study, each animal was used only once.

DATA ANALYSIS

To evaluate the effects of volatile anaesthetics on nitrous oxide or morphine analgesia, a regression line of the log doses of a volatile anaesthetic *vs* tail-flick latency MPE values was first constructed by the least square method for each combination of anaesthetics. The IC_{50} (the inspired concentration of a volatile anaesthetic which produces 50 % attenuation of nitrous oxide or morphine-induced analgesia) and 95 % confidence intervals were then calculated. Analysis of variance (ANOVA) was used to compare the effect of halothane, isoflurane or 100 % oxygen alone on TFL. ANOVA and Dunnett's test were used to compare physiological data from animals that received volatile anaesthetics with nitrous oxide or morphine with data from those that received nitrous oxide or morphine alone. $P < 0.05$ was considered significant.

Results

Nitrous oxide 75 % increased tail-flick latency (mean MPE 37 (SEM 5) %) but 0.5 MAC of halothane or isoflurane did not alter the response (MPE −4.1 (2) % and −1.5 (1) %, respectively; $F = 0.89$, df = 2 and 13, $P > 0.20$). Both volatile anaesthetics dose-dependently antagonized nitrous oxide analgesia (fig. 1A) and halothane was more potent than isoflurane in this regard. Halothane doses as low as 0.1 and 0.2 MAC produced 76 % and 107 % antagonism of nitrous oxide analgesia, respectively; as the antagonism produced by the lowest concentration was greater than 50 %, we could only estimate an IC_{50} of < 0.1 MAC (confidence level 95 %). Isoflurane 0.5 MAC also induced almost complete (85 %) antagonism, but lower doses were less effective (IC_{50} = 0.23 MAC; 95 % confidence interval 0.18–0.30 MAC).

By design, morphine 1.25 mg kg^{-1} alone prolonged tail-flick latency to the same extent as 75 % nitrous oxide (MPE 35 (9) %). Halothane dose-dependently antagonized this morphine analgesia, with 0.7 MAC producing 80 % antagonism (IC_{50} = 0.43 MAC; 95 % confidence interval 0.36–0.51 MAC) (fig. 1B).

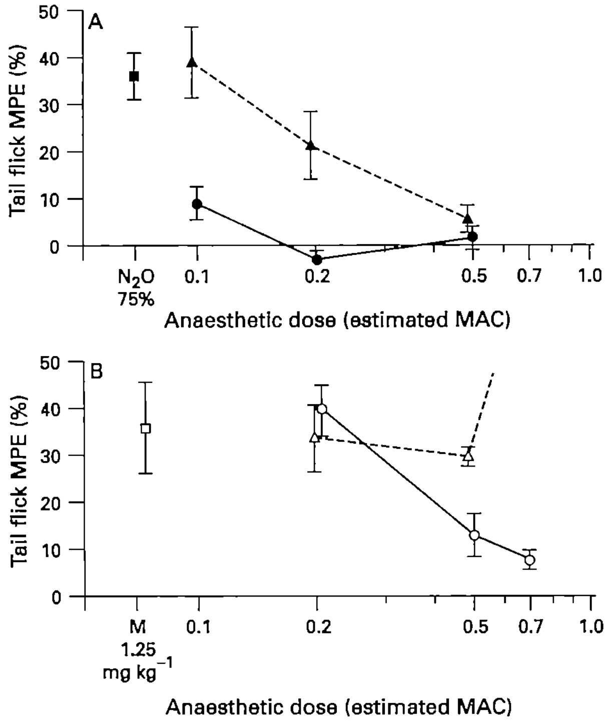


Figure 1 Effect of volatile anaesthetics on nitrous oxide (N_2O) or morphine-induced analgesia. Tail-flick testing was performed twice each before and 20 min after the start of anaesthesia, and the measured latencies were converted to maximum percentage effect (MPE) according to the formula described in the text. (A) N_2O–halothane (●) and N_2O–isoflurane (▲) interactions. (B) Morphine–halothane (○) and morphine–isoflurane (△) interactions. Anaesthetic dose is the dose of volatile anaesthetic added to N_2O or morphine, respectively. The combination of morphine and 0.7 MAC of isoflurane prolonged the tail-flick latency above the cut-off time (i.e. MPE > 100%) in all animals. Data are mean, SEM for 4–14 animals per group (see text).

In contrast, isoflurane did not attenuate morphine analgesia at either 0.2 or 0.5 MAC and, at 0.7 MAC, prolonged tail-flick latency beyond the cut-off time (MPE > 100%; fig. 1B). However, 0.7 MAC of isoflurane combined with morphine also produced some degree of motor dysfunction (i.e. mild flaccidity with some impairment of weight-bearing), suggesting that the prolonged tail-flick response may not be caused entirely by the antinociceptive effects of these agents.

Halothane did not alter tail temperature, whereas isoflurane in combination with nitrous oxide reduced it slightly ($P < 0.05$; table 1). MAP was lower in rats that received a volatile anaesthetic but remained within the physiological range. Morphine-treated rats became hypercapnic and halothane, but not isoflurane, increased Pa_{CO_2} slightly in both nitrous oxide and morphine-treated animals (table 1).

Discussion

We have demonstrated that sub-MAC concentrations of volatile anaesthetics dose-dependently antagonized the analgesic action of nitrous oxide, and that halothane was more potent than isoflurane. In addition, halothane antagonized morphine-induced analgesia in a dose-dependent manner, whereas isoflurane has no effect. As higher doses of halothane were required to antagonize morphine compared with nitrous oxide analgesia, and isoflurane antagonized the effect of nitrous oxide but not morphine, we conclude that nitrous oxide was more sensitive than morphine to analgesic antagonism by volatile anaesthetics.

In previous work using the formalin test to assess nociception [1], we demonstrated that nitrous oxide analgesia can be antagonized by halothane, and these results have been reproduced recently by others [13]. Antagonism between nitrous oxide and volatile anaesthetics has also been reported for MAC in the rat [8, 14] and suppression of learning in humans [15], although interpretation of the MAC studies is a subject of much debate [16–18]. Similarly, a marked morphine–halothane antagonism has been reported for the escape reaction threshold to tail pressure [19] and the cardiac acceleration response to tail clamp [20] in the rat, but the agents were additive in suppressing noxious stimulation-induced purposeful movements [20]. Thus the nature of these drug interactions may vary with the end-point.

It appears unlikely that alterations in physiological variables account for the observed antagonism between the volatile anaesthetics and nitrous oxide or morphine. The isoflurane-induced decrease in tail skin temperature cannot account for attenuation of nitrous oxide analgesia as tail hypothermia has the opposite effect (i.e. prolongs tail-flick latency) [10]. However, the fact that isoflurane, but not halothane, reduced tail skin temperature may be at least partially responsible for the weaker antagonism of nitrous oxide or morphine analgesia produced by isoflurane than halothane. Similarly, moderate hypercapnia (Pa_{CO_2} 8.0–13.3 kPa) prolongs tail-flick latency [11], and therefore slight increases in Pa_{CO_2} produced by the addition of halothane would be expected to intensify, rather than antagonize, nitrous oxide and morphine analgesia. With respect to arterial pres-

Table 1 Physiological data (mean (SEM)) for eight (nitrous oxide (N_2O) or morphine alone groups) or four (combination groups) animals. Data of animals that received the combination of volatile anaesthetic and N_2O or morphine were compared with those that received N_2O or morphine, alone respectively, by ANOVA and Dunnett's test. *$P < 0.05$, **$P < 0.01$

Anaesthesia	MAP (mm Hg)	Tail temp (°C)	pH	Pa_{CO_2} (kPa)	Pa_{O_2} (kPa)
N_2O	138 (1)	28.5 (0.5)	7.42 (0.01)	5.3 (0.1)	16.8 (0.4)
N_2O + halothane	123 (4)**	28.1 (0.6)	7.38 (0.01)*	5.8 (0.1)**	16.7 (0.9)
N_2O + isoflurane	111 (2)**	25.8 (0.2)**	7.43 (0.02)	4.9 (0.4)	17.2 (0.7)
Morphine	136 (2)	26.3 (0.4)	7.36 (0.01)	6.3 (0.1)	60.3 (1.2)
Morphine + halothane	125 (5)*	26.8 (0.7)	7.29 (0.02)**	7.0 (0.2)	64.3 (0.9)
Morphine + isoflurane	110 (2)**	25.7 (0.2)	7.38 (0.01)	6.2 (0.2)	61.9 (1.2)

sure, hypertension is known to produce antinociception [12], but we know of no data on the effect of hypotension. If a mild decrease in arterial pressure were the mechanism underlying antagonism of nitrous oxide and morphine analgesia by volatile anaesthetics, isoflurane should produce greater antagonism than halothane because arterial pressure was lower with isoflurane. This again contradicts our results.

Although neither halothane nor isoflurane alone altered tail-flick latency, these anaesthetics could have intrinsic hyperalgesic properties. In fact, halothane has been reported to slightly decrease the pain threshold to pressure in humans [21]. In our study, the short baseline tail-flick latency caused by intense heat stimuli might have obscured such effects. However, studies with tail-flick testing with a longer baseline latency (5–6 s) have shown that sub-MAC concentrations of halothane and isoflurane modestly prolong tail-flick latency in rodents [22, 23]. In addition, the volatile agents inhibit noxious heat-evoked firing of spinal wide dynamic range nociceptive neurones *in vivo* [24] and suppress electrical stimulation-induced nociceptive transmission in the spinal cord *in vitro* [25]. Hence, it is unlikely that the hyperalgesic properties of the volatile anaesthetics explain the observed antagonism between volatile agents and nitrous oxide or morphine. It is also not likely that volatile anaesthetics possess opioid antagonist properties as, although both morphine and nitrous oxide activate opioid receptors either directly or indirectly [1, 3], halothane does not displace specific binding of radiolabelled ligands to either μ or κ receptor subtypes *in vitro* [26, 27]. We have postulated previously, however, that volatile anaesthetics may antagonize analgesia by a metabolic mechanism [1]. Nitrous oxide and morphine analgesia require active neural processes, including activation of a descending inhibitory pathway [28, 29]. Thus by decreasing the cerebral or spinal metabolic rate, halothane or isoflurane could prevent such neural activation. Although unproved, this hypothesis could explain why nitrous oxide is more susceptible than morphine to antagonism by volatile anaesthetics; spinal transection studies suggest that a descending inhibitory pathway plays a more important role in mediating nitrous oxide than morphine analgesia [28, 29].

Although tail-flick testing is a widely accepted measure of analgesia in animals, extrapolation of these results to the clinical setting requires caution. First, as the MAC of nitrous oxide in rats is 148–235 % [18, 30, 31], we have used only 0.3–0.5 MAC of nitrous oxide, which is lower than that usually administered clinically. It is natural to speculate that the analgesic effect of higher doses of nitrous oxide or morphine may be more resistant to antagonism by volatile anaesthetics. In fact, profound analgesia produced by morphine 10 mg kg^{-1} i.v. (the tail-flick MPE $> 100\%$) was not affected by up to 1 MAC of halothane [unpublished observation]. Second, the tail-flick response is a spinal reflex [4] and such measures are not used clinically to evaluate the adequacy of anaesthesia, analgesia, or both. Third, as discussed previously, the nature of the interaction among anaesthetics appears to vary for different end-points [1, 8, 14, 19, 20]; integrated, complex pain processes may be affected differently than a spinal reflex. Nevertheless, our experiments demonstrate that a simple relationship between anaesthesia and analgesia cannot be assumed because addition of a volatile anaesthetic to nitrous oxide or morphine, while deepening anaesthesia, resulted in less profound analgesia. Thus anaesthesia and analgesia are different end-points and should be considered separately.

Acknowledgement

Supported in part by NIGMS grant RO1 GM4 2466 to G.C.

References

1. Goto T, Marota JJA, Crosby G. Nitrous oxide induces pre-emptive analgesia in the rat that is antagonized by halothane. *Anesthesiology* 1994; **80**: 409–416.
2. Abram SE, Yaksh TL. Morphine, but not inhalational anesthesia, blocks postinjury facilitation: The role of pre-emptive suppression of afferent transmission. *Anesthesiology* 1993; **78**: 713–721.
3. Gillman MA. Analgesic (sub anaesthetic) nitrous oxide interacts with the endogenous opioid system: a review of the evidence. *Life Sciences* 1986; **39**: 1209–1221.
4. Irwin S, Houde RW, Bennett DR, Hendershot LC, Seevers MH. The effects of morphine, methadone and meperidine on some reflex responses of spinal animals to nociceptive stimulation. *Journal of Pharmacology and Experimental Therapeutics* 1951; **101**: 132–143.
5. Ding XH, Ji XQ, Tsou K. Pentobarbital selectively blocks supraspinal morphine analgesia. Evidence for $GABA_A$ receptor involvement. *Pain* 1990; **43**: 371–376.
6. Frederickson RC, Burgis V, Edwards JD. Hyperalgesia induced by naloxone follows diurnal rhythm in responsivity to painful stimuli. *Science* 1977; **198**: 756–758.
7. White PF, Johnston RR, Eger EI II. Determination of anesthetic requirement in rats. *Anesthesiology* 1974; **40**: 52–57.
8. Cole DJ, Kalichman MW, Shapiro HM, Drummond JC. The nonlinear potency of sub-MAC concentrations of nitrous oxide in decreasing the anesthetic requirement of enflurane, halothane, and isoflurane in rats. *Anesthesiology* 1990; **73**: 93–99.
9. Mazze RI, Rice SA, Baden JM. Halothane, isoflurane, and enflurane MAC in pregnant and nonpregnant female and male mice and rats. *Anesthesiology* 1985; **62**: 339–341.
10. Hole K, Tjølsen A. The tail-flick and formalin tests in rodents: changes in skin temperature as a confounding factor. *Pain* 1993; **53**: 247–254.
11. Gamble GD, Milne RJ. Hypercapnia depresses nociception: endogenous opioids implicated. *Brain Research* 1990; **514**: 198–205.
12. Thurston CL, Randich A. Acute increases in arterial blood pressure produced by occlusion of the abdominal aorta induces antinociception: peripheral and central substrates. *Brain Research* 1990; **519**: 12–22.
13. O'Connor TC, Abram SE. Inhibition of nociception-induced spinal sensitization by anesthetic agents. *Anesthesiology* 1995; **82**: 259–266.
14. Cole DJ, Kalichman MW, Shapiro HM. The nonlinear contribution of nitrous oxide at sub-MAC concentrations to enflurane MAC in rats. *Anesthesia and Analgesia* 1989; **68**: 556–562.
15. Chorkoff BS, Bennett HL, Eger EI II. Does nitrous oxide antagonize isoflurane-induced suppression of learning? *Anesthesiology* 1993; **79**: 724–732.
16. Eger EI II. Does 1+1 = 2? *Anesthesia and Analgesia* 1989; **68**: 551–555.
17. Cole DJ, Kalichman MW, Shapiro HM, Eger EI II. Does 1+1 = 2?—a continuing debate. *Anesthesia and Analgesia* 1990; **70**: 126–127.

18. Gonsowski CT, Eger EI II. Nitrous oxide minimum alveolar anesthetic concentration in rats is greater than previously reported. *Anesthesia and Analgesia* 1994; **79**: 710–712.
19. Kissin I, Jebeles JA. Halothane antagonizes effect of morphine on the motor reaction threshold in rats. *Anesthesiology* 1984; **61**: 671–676.
20. Kissin I, Kerr CR, Smith LR. Morphine–halothane interaction in rats. *Anesthesiology* 1984; **60**: 553–561.
21. Dundee JW, Nichol RM, Black GW. Alterations in response to somatic pain associated with anaesthesia. X: Further studies with inhalation agents. *British Journal of Anaesthesia* 1962; **34**: 158–160.
22. Deady JE, Koblin DD, Eger EI II, Heaver JE, D'Aoust B. Anesthetic potencies and the unitary theory of narcosis. *Anesthesia and Analgesia* 1981; **60**: 380–384.
23. Levin LL, Winter PM, Nemoto EM, Uram M, Lin MR. Naloxone does not antagonize the analgesic effects of inhalation anesthetics. *Anesthesia and Analgesia* 1986; **65**: 330–332.
24. Namiki A, Collins JG, Kitahata LK, Kikuchi H, Homma E, Thalhammer JG. Effects of halothane on spinal neuronal responses to graded noxious heat stimulation in the cat. *Anesthesiology* 1980; **53**: 475–480.
25. Savola MK, Woodley SJ, Maze M, Kendig J. Isoflurane and an alpha$_2$-adrenoceptor agonist suppress nociceptive neurotransmission in neonatal rat spinal cord. *Anesthesiology* 1991; **75**: 489–498.
26. Inoki R, Kim SY, Maeda S, Nakamae J, Mashimo T, Yoshiya I. Effect of inhalational anaesthetics on the opioid receptors in the rat brain. *Life Sciences* 1983; 33 (Suppl. I): 223–226.
27. Lawrence D, Livingston A. Opiate-like analgesic activity in general anaesthetics. *British Journal of Pharmacology* 1981; **73**: 435–442.
28. Hanaoka K, Ohtani M, Toyooka H, Dohi S, Ghazi-saidi K, Taub A, Kitahata LM. The relative contribution of direct and supraspinal descending effects upon spinal mechanisms of morphine analgesia. *Journal of Pharmacology and Experimental Therapeutics* 1978; **207**: 476–484.
29. Komatsu T, Shingu K, Tomemori N, Urabe N, Mori K. Nitrous oxide activates the supraspinal pain inhibition system. *Acta Anaesthesiologica Scandinavica* 1981; **25**: 519–522.
30. Russel GB, Graybeal JM. Direct measurement of nitrous oxide MAC and neurologic monitoring in rats during anesthesia under hyperbaric conditions. *Anesthesia and Analgesia* 1992; **75**: 995–999.
31. Wardley-Smith B, Halsey MJ. Mixtures of inhalation and i.v. anaesthetics at high pressure. *British Journal of Anaesthesia* 1985; **57**: 1248–1256.

British Journal of Anaesthesia 1996; **76**: 707–712

Effect of low-dose dopamine on intestinal villus microcirculation during normotensive endotoxaemia in rats

H. SCHMIDT, A. SECCHI, R. WELLMANN, H. BÖHRER, A. BACH AND E. MARTIN

Summary

Hypoperfusion of the gut mucosa is thought to be a factor in the development of gut barrier failure during sepsis and septic shock. Dopamine stimulates DA-1 receptors which mediate regional vasodilatation in the gut. Therefore, we have investigated the effect of low-dose dopamine (3 μg kg^{-1} min^{-1}) on the intestinal villus microcirculation during endotoxaemia in a rat model of normotensive endotoxaemia, using *in vivo* videomicroscopy. Blood flow in and the diameters of central villus arterioles were measured before, immediately after and 60 min after a 1-h continuous infusion of endotoxin 1.5 mg/kg body weight. After baseline measurements were obtained, rats received either an infusion of 0.9% saline (group A; $n = 7$) or a volume-equivalent infusion of dopamine 3 μg kg^{-1} min^{-1} (group B; $n = 7$) throughout the study. Control animals (group C; $n = 7$) received no endotoxin or dopamine. In group A, villus blood flow (mean baseline 8.4 (SEM 0.9) nl min^{-1}) decreased by 29.7 (8.9)% to 5.9 (0.9) nl min^{-1} immediately after endotoxin challenge and by a total of 43.1 (7.3)% to 4.7 (0.7) nl min^{-1} after another 60 min. Simultaneously, villus arteriolar diameters decreased from 7.8 (0.2) to 6.9 (0.3) μm and to 6.5 (0.3) μm, respectively. In group B, villus blood flow (baseline 8.7 (0.4) nl min^{-1}) was unchanged immediately after the 1-h infusion of endotoxin (8.3 (0.4) nl min^{-1}). However, another 60 min later blood flow decreased by 28.8 (8.0)% to 6.1 (0.7) nl min^{-1}. In contrast with group A, the diameters of the central villus arterioles were unchanged despite administration of endotoxin (7.9 (0.2) μm; 8.1 (0.4) μm; 8.2 (0.5) μm). In group C, there were no changes in villus blood flow or arteriolar diameters throughout the study. Our results indicated that low-dose dopamine did not prevent, but delayed and attenuated, the decrease in intestinal villus blood during normotensive endotoxaemia. (*Br. J. Anaesth.* 1996; **76**: 707–712)

Key words

Sympathetic nervous system, dopamine. Complications, endotoxaemia. Gastrointestinal tract, intestine. Blood, flow, mucosal. Rat.

The gut mucosa functions as an important barrier preventing translocation of intraluminal bacteria and toxins into the systemic circulation [1]. However, there is an increase in intestinal permeability and translocation during sepsis and endotoxaemia [2–4]. Thus gut-derived endotoxaemia and bacteraemia might be responsible for a self-maintaining process of sepsis and septic shock, and the development of multiple organ failure [5, 6]. Among other pathophysiological mechanisms, hypoperfusion of the gut mucosa has been implicated as an important mechanism contributing to endotoxin-induced mucosal injury [7, 8]. Xu and colleagues [8] described a selective reduction in intestinal blood flow to the distal ileum and caecum by 35–50 % in a rat model of hyperdynamic endotoxaemia which was associated with an increase in small bowel permeability to ^{51}Cr-EDTA.

The development of intestinal hyperpermeability after endotoxin challenge is prevented by maintenance of gut perfusion [9]. In critically ill patients, low-dose dopamine is used for improvement in splanchnic blood flow, particularly to optimize renal perfusion [10]. In patients undergoing gastrectomy, administration of low-dose dopamine (3 μg kg^{-1} min^{-1}) improves portal venous oxygenation suggesting an increase in splanchnic blood flow [11]. In contrast, low-dose dopamine has been demonstrated to exacerbate gut ischaemia during experimental haemorrhagic shock [12]. There are no *in vivo* data during sepsis and septic shock on the influence of low-dose dopamine on the intestinal microcirculation. Therefore, we have investigated the effects of low-dose dopamine on blood flow and arteriolar diameters in intestinal villi in a model of normotensive endotoxaemia in rats.

Materials and methods

ANIMAL PREPARATION

The study protocol was approved by the Governmental Animal Protection Committee. We used male Wistar rats (250–300 g body weight) that were fasted overnight, but received water *ad libitum*. Anaesthesia was induced with sodium pentobarbitone 60 mg/kg body weight i.p. which was supplemented with i.m. injection of 30 mg/kg body weight, 30 min before the start of *in vivo* microscopy. Polyethylene

---

HEINFRIED SCHMIDT, MD, DEAA, ANDREAS SECCHI, MD, RUTH WELLMANN, HUBERT BÖHRER, MD, DEAA, ALFONS BACH, MD, EIKE MARTIN, MD, FANZCA, Department of Anaesthesiology, University of Heidelberg, D-69120 Heidelberg, Germany. Accepted for publication: December 12, 1995.

Correspondence to H.S.

catheters (od 0.8 mm, id 0.5 mm) were inserted into the jugular vein for administration of endotoxin and infusion of dopamine or 0.9% saline, and into the carotid artery for blood sampling and measurement of systemic arterial pressure. Heart rate was derived from the pressure signal. A tracheotomy was performed for airway control. Animals breathed room air. Rectal temperature was maintained at 37 °C using a heating lamp.

Intravital microscopy of the intestinal villus microcirculation was performed according to the method described by Gore and Bohlen [13, 14]. A small segment (2 cm) of the terminal ileum was exteriorized through an abdominal midline incision, opened along its antimesenteric border using electrocautery and placed on a transparent viewing pedestal with the mucosa being upward. After fixation to a frame by four sutures (Ethilon II, 0.7 metric; Ethicon, Germany) the opened bowel segment was placed in a temperature-controlled chamber containing a solution of bicarbonate-buffered Ringer's solution (37.0 °C). The animal was then transferred to the stage of the microscope. The opened mucosal surface was superfused with thermostatically controlled bicarbonate-buffered Ringer's solution that slowly rinsed from the top of the objective of the microscope onto the mucosa. This solution was equilibrated with 5% carbon dioxide in nitrogen to adjust the pH to 7.35, $P\text{O}_2$ to 3.7–4.0 kPa and $P\text{CO}_2$ to 4.8–5.6 kPa. In each rat, 0.5 ml/kg body weight of fluorescent labelled erythrocytes (packed cell volume (PCV) 50%) from donor rats was injected i.v., 30 min before microscopy.

INTRAVITAL MICROSCOPY

The villus microcirculation was observed using transillumination and epifluorescence illumination. Five successive fields of the mucosa were viewed and videotaped for 40 s each. The villus central arterioles were identified according to a descriptive classification [13] and assessment of flow direction in the vessels. The equipment for intravital microscopy consisted of a specially designed intravital microscope (Leitz, Germany) equipped with a ×25 water immersion objective (PL Fluotar 25/0.75 W; Leitz, Germany). Epifluorescence illumination was performed using an epifluorescence illuminator (Leitz; Germany) equipped with an XBO 100 W/2 short arc mercury lamp (Osram, Germany) and an excitation filter (450–490 nm). Transillumination was achieved using a 100 W cold light fountain (KL1500 electronic; Schott, Germany). The microscopic images were transferred to a monitor (PVM/444QM; Sony, Japan) by a low-light camera (CF 8/1; Kappa, Germany) and videotaped for subsequent off-line analysis.

FLUORESCENT LABELLING OF ERYTHROCYTES

Erythrocytes from separate donor animals were labelled with fluorescein isothiocyanate (FITC, Isomer I, No. F-7250; Sigma Chemicals, Germany) using a modified procedure according to Butcher and Weissman [15] and Sarelius and Duling [16]. Erythrocytes were washed three times in a glucose–saline buffer (pH 8.2), resuspended in a bicine–saline buffer (pH 6.8) containing FITC 9 mg ml^{-1} and incubated at 25 °C for 3 h. Labelled cells were then separated from the solution, washed several times until the supernatant was free from fluorescent dye, resuspended in 0.9% NaCl containing 14% citrate–phosphate–glucose (No. C-7165; Sigma Chemicals, Germany) and stored at 1–4 °C in the dark. Using this method, there was no reduction in fluorescence for 7 days. Normal rheological behaviour of FITC-labelled erythrocytes *in vivo* in the rat has been demonstrated by Sarelius and Duling [16]. The *in vivo* stability of FITC-labelled erythrocytes during a 12-h period in rats has been confirmed by Mithöfer and colleagues [17].

DETERMINATION OF INTESTINAL VILLUS BLOOD FLOW AND VILLUS ARTERIOLAR DIAMETERS

Villus blood flow was measured using a combined approach of the methods described by Chun and colleagues [18] for determination of villus red cell flux, and Mithöfer and colleagues [17] for calculation of volumetric blood flow using FITC-labelled erythrocytes. In order to calculate volumetric blood flow in the central villus arteriole, the flux of labelled erythrocytes circulating through the central arteriole near the tip of the villus was determined by videotape replay on a monitor screen during a 30-s period by an observer who was unaware of the identify of the experimental group. The flux of labelled cells (J_{FITC}) per five fields per observation period was averaged in order to rule out time-dependent changes in arteriolar blood flow. Furthermore, at each observation time, arterial blood samples were obtained and the concentration of labelled erythrocytes per unit volume of arterial blood (N_{FITC}) was determined using a Neubauer chamber (Hecht, Germany). Volumetric blood flow in the villus arteriole was calculated from the ratio $J_{\text{FITC}}/N_{\text{FITC}}$. However, because systemic PCV differs from PCV in microcirculatory vessels because of the Fahraeus effect [19], the calculated volumetric blood flow has to be corrected by a factor of 0.76[20]. Therefore, volumetric blood flow (V) in the villus arterioles was calculated as $V = (J_{\text{FITC}}/N_{\text{FITC}})/0.76$ (nl min^{-1}). The diameters of the central villus arterioles were measured using a computerized microcirculation analysis system (Cap image; Zeintl, Germany).

MONITORING

Mean arterial pressure and heart rate were recorded simultaneously with measurement of the intestinal villus microcirculation. In addition, arterial blood samples were obtained to measure PCV (Hematology Analyzer System CP 9000-3; Serono-Baker-Diagnostics Inc., USA) and to perform blood-gas analysis (ABL3; Radiometer, Denmark).

PROCEDURE

The rats were allocated randomly to one of three groups, each group containing seven animals: group A, endotoxin infusion alone (1.5 mg kg^{-1} h^{-1};

Escherichia coli 026:B6; Sigma Chemicals, Germany) from $t = 0$ min to $t = 60$ min; group B, dopamine-treated rats. Endotoxin infusion as in group A, and dopamine infusion (3 μg kg^{-1} min^{-1}) from $t = 0$ min to $t = 120$ min. Dopamine (dopamine hydrochloride; Giulini Pharma, Hannover, Germany) was diluted in 0.9 % saline; group C, control rats. The control rats were given only 0.9 % saline from $t = 0$ min to $t = 120$ min.

During the study all rats received the same amount of fluid, with an infusion rate of 15 ml kg^{-1} h^{-1}. After placing the animals beneath the microscope and injection of fluorescent-labelled erythrocytes, a stabilization period of 30 min was allowed. Videomicroscopy for measurement of villus blood flow, blood sampling for evaluation of PCV and blood-gas analysis, and measurement of haemodynamic variables were performed at $t = 0$ min, $t = 60$ min and $t = 120$ min. Infusion of endotoxin (groups A and B) and dopamine was started after measurement of baseline values ($t = 0$ min).

STATISTICAL ANALYSIS

Data are presented as mean (SEM) unless otherwise indicated. For statistical analysis, the values of five villi were averaged for each animal, and the means were used for further calculations. Differences within and between groups were analysed using two-way ANOVA followed by the Scheffé test. $P < 0.05$ was considered significant.

Results

The age and weight of the animals did not differ between groups. Signs of infection or sepsis were not observed in any of the animals before the experimental procedure.

SYSTEMIC VARIABLES

At the start of the experiment, cardiorespiratory variables did not differ between groups. Mean arterial pressure remained unchanged throughout the observation period in all groups. However, heart rate increased in both groups challenged with endotoxin (groups A and B). Dopamine had no effect on mean arterial pressure or heart rate in group B compared with group A. There were no changes in Po_2 or pH throughout the study in any group. In all groups, there was a reduction in Pco_2 during the study but this was not significant. PCV values showed no difference between the groups at the start of the experiment and were unaffected in all groups throughout the study (table 1).

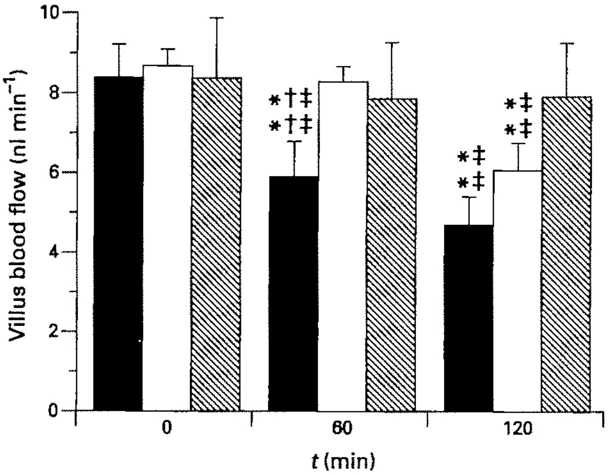


Figure 1 Intestinal villus blood flow at baseline ($t = 0$ min), 60 min ($t = 60$ min) and 120 min ($t = 120$ min) after starting the experiment in group A (■) (endotoxin 1.5 mg kg^{-1} from $t =$ 0 min until $t = 60$ min), group B (□) (endotoxin 1.5 mg kg^{-1} from $t = 0$ min until $t = 60$ min and dopamine 3 μg kg^{-1} min^{-1} from $t = 0$ min until $t = 120$ min) and group C (▨) (0.9 % saline from $t = 0$ min until $t = 120$ min). All data are mean, SEM. ** $P < 0.01$ *vs* baseline, †† $P < 0.01$ *vs* group B, ‡‡ $P < 0.05$ *vs* group C.

ALTERATIONS IN INTESTINAL VILLUS MICROCIRCULATION

Changes in villus blood flow and villus arteriolar diameters are shown in figures 1 and 2. Baseline values of villus blood flow did not differ between groups (group A, 8.4 (0.8) nl min^{-1}; group B, 8.7 (0.4) nl min^{-1}; group C, 8.4 (1.5) nl min^{-1}). Furthermore, there were no differences in the diameters of the villus arterioles between groups at the start of the experiment (group A, 7.8 (0.2) μm, group B, 7.9 (0.2) μm; group C, 7.6 (0.3) μm). Infusion of endotoxin in group A led to a decrease in blood flow in the

Table 1 Mean (SEM) changes in cardiorespiratory variables during the experiments in group A (endotoxin 1.5 mg kg^{-1} from $t = 0$ min until $t = 60$ min), group B (endotoxin 1.5 mg kg^{-1} from $t = 0$ min until $t = 60$ min and dopamine 3 μg kg^{-1} min^{-1} from $t = 0$ min until $t = 120$ min) and group C (0.9 % saline from $t = 0$ min until $t = 120$ min). * $P < 0.01$ *vs* baseline, †† $P < 0.01$ *vs* group C

Time (min)	Group	MAP (mm Hg)	HR (beat min^{-1})	pH	Pco_2 (kPa)	Po_2 (kPa)	PCV (%)
0	A	129 (2)	386 (10)	7.32 (0.01)	5.8 (0.1)	12.8 (0.4)	41.3 (0.8)
	B	136 (6)	381 (11)	7.31 (0.02)	5.5 (0.3)	11.3 (1.5)	42.6 (0.8)
	C	126 (6)	390 (21)	7.35 (0.02)	5.5 (0.3)	12.4 (0.8)	42.3 (1.7)
60	A	121 (7)	405 (17)	7.37 (0.02)	5.1 (0.3)	13.5 (1.2)	43.1 (0.7)
	B	134 (3)	407 (11)	7.32 (0.02)	4.7 (0.1)	11.7 (1.1)	42.0 (0.9)
	C	125 (8)	385 (18)	7.37 (0.03)	4.9 (0.3)	12.7 (0.8)	41.3 (2.4)
120	A	123 (4)	441 (14)**††	7.36 (0.01)	4.7 (0.1)	13.5 (0.3)	41.3 (1.4)
	B	126 (4)	437 (6)**††	7.29 (0.02)	4.5 (0.3)	13.1 (0.4)	40.0 (0.9)
	C	119 (7)	395 (11)	7.38 (0.04)	4.5 (0.1)	13.7 (0.5)	39.1 (2.1)

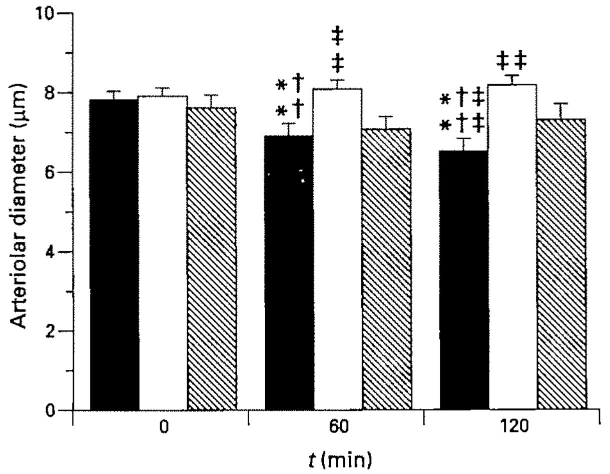


Figure 2 Diameters of the central villus arteriole at baseline ($t = 0$ min), 60 min ($t = 60$ min) and 120 min ($t = 120$ min) after the start of the experiment in group A (■) (endotoxin 1.5 mg kg^{-1} from $t = 0$ min until $t = 60$ min), group B (□) (endotoxin 1.5 mg kg^{-1} from $t = 0$ min until $t = 60$ min and dopamine 3 µg kg^{-1} min^{-1} from $t = 0$ min until $t = 120$ min) and group C (▧) (0.9 % saline from $t = 0$ min until $t = 120$ min). All data are mean, SEM. ** $P < 0.01$ *vs* baseline, †† $P < 0.01$ *vs* group B, ‡‡ $P < 0.01$ *vs* group C.

central villus arterioles to 5.9 (0.9) nl min^{-1} at $t = 60$ min, which was a reduction of 29.7 (8.9)% ($P < 0.01$). Sixty minutes after cessation of administration of endotoxin ($t = 120$), blood flow was diminished by 43.1% from baseline to 4.7 (0.7) nl min^{-1} ($P < 0.01$). This reduction in villus blood flow was associated with a decrease in arteriolar diameters of 11.8 (1.1)% and 15.9 (2.4)%, respectively ($P < 0.01$). In contrast, in the dopamine group (group B) blood flow in the villus arterioles remained unchanged at $t = 60$ min (−2.7 (5.4)%; 8.3 (0.4) nl min^{-1}; $P > 0.05$). However, at $t =$ 120 min blood flow was reduced by 28.8 (8.0)% from baseline (6.1 (0.7) nl min^{-1}; $P < 0.01$). In contrast with group A, there was no vasoconstriction of the villus arteriolar diameters in the dopamine group at any time. Arteriolar diameters in the dopamine group increased significantly at $t = 60$ min and $t = 120$ min compared with groups A and C. In control animals (group C) which received no endotoxin or dopamine, there were no alterations in villus blood flow or arteriolar diameters throughout the study.

Discussion

We found that a continuous infusion of endotoxin resulted in a decrease in intestinal villus blood flow associated with a decrease in central villus arteriole diameter, despite normotensive macrocirculatory conditions. In rats given endotoxin, villus blood flow decreased by 29.7 (8.9)% after 60 min and by 43.1 (7.3)% after 120 min after the start of the endotoxin challenge. This reduction in villus blood flow was associated with vasoconstriction of the central villus arteriole by 11.8 (1.1)% and 15.9 (2.4)%, respectively. These results are in agreement with those obtained by other groups [21, 22] who demonstrated a reduction in segmental mesenteric blood flow which was accompanied by constriction of the previllus microcirculation in the submucosal layer of the bowel wall in a normotensive model of live *E. coli* bacteraemia in rats.

Endotoxin-induced intestinal damage is limited to the mucosa, especially to the villus tips [23, 24]. The preferential sensitivity of the villus tip to hypoperfusion and ischaemic injury is related to its peculiar vascular anatomy. The microcirculation of the intestinal villus is characterized by a central arteriole which branches near the tip of the villus into a subepithelial network of capillaries which drain into venules. Because of the close proximity of the ascending arteriole and the descending venule, a countercurrent arteriovenous diffusion of oxygen occurs resulting in low $P\text{O}_2$ values at the tip of the villus [25, 26]. Using a mathematical model of the countercurrent oxygen exchange mechanism in the intestinal villus, a blood flow-dependent decrease in the villus tip has been demonstrated [27]. Furthermore, the mucosa represents the major site of oxygen consumption in the gut and thus it is to be expected that the mucosa would also be the most susceptible portion of the gut wall to impaired oxygen delivery [28]. Impairment of the mucosal microcirculation characterized by a decrease in villus blood flow during endotoxaemia, as demonstrated in our study, might therefore account for the development of endotoxin-associated mucosal lesions observed in animals with normal blood flow in the mesenteric artery [29].

Maintenance of gut perfusion has been shown to avoid the increase in intestinal hyperpermeability [9] in a model of hyperdynamic endotoxaemia in pigs. Furthermore, increased permeability to large molecules suggesting loss of intercellular tight junction integrity represents the earliest manifestation of splanchnic ischaemia [30].

In humans, improved survival of critically ill patients has been demonstrated when a decrease in gastric mucosal pH is prevented, thus avoiding splanchnic hypoxia [31]. Therefore, maintenance of intestinal mucosal perfusion appears to be important for the prevention of gut-derived mortality in critically ill and septic patients. In critically ill patients, low-dose dopamine is often used to improve splanchnic blood flow, especially to optimize renal perfusion [10, 32]. However, the effects of low-dose dopamine on the mesenteric microcirculation during several pathophysiological conditions are contradictory. On the one hand, administration of low-dose dopamine (3 µg kg^{-1} min^{-1}) during gastrectomy improves portal venous oxygenation suggesting an increase in splanchnic blood flow [11]. In addition, it improves portal flow and gut oxygen delivery during PEEP ventilation in a model of acute lung injury [33]. On the other hand, low-dose dopamine has been demonstrated to exacerbate gut ischaemia in a porcine model of haemorrhagic shock [12]. Furthermore, low-dose dopamine worsens intestinal ischaemia during experimental flow reduction in the superior mesentery artery [34]. Pawlik and colleagues [35] described a reduction in mesenteric blood flow, intestinal oxygen consumption and intestinal capillary density in anaesthetized dogs induced by low (1 μg kg^{-1} min^{-1}), intermediate (5 μg kg^{-1} min^{-1}) and high (20 μg kg^{-1} min^{-1}) doses of dopamine. They suggested from these results that dopamine caused smooth muscle contraction in mesenteric arterioles and precapillary sphincters, thereby reducing total blood flow by constricting arterioles and reducing the nutrient circulation by closing capillaries.

In our study, administration of low-dose dopamine prevented constriction of the villus arteriolar microcirculation during endotoxaemia. The arteriolar diameters in endotoxaemic rats increased during infusion of dopamine even compared with non-endotoxic control animals. Because blood flow in the splanchnic bed is partially under dopaminergic control [36], dilatation of the intestinal villus arterioles can be explained by stimulation of dopamine (DA)-1 receptors. Sixty minutes after the start of the infusion of endotoxin, low-dose dopamine maintained intestinal villus perfusion at baseline levels and prevented the decrease observed during endotoxaemia. However, 120 min after the start of the endotoxin infusion, villus blood flow decreased despite the vasodilator effect of the administered dopamine. This disparity might be explained by simultaneous dilatation of shunt vessels between fourth-order arterioles and fourth-order venules which are located in the previllus, submucosal microcirculation [13]. Thus increased shunting of blood on the previllus level might occur which then does not participate in mucosal perfusion.

In conclusion, our study has demonstrated that low-dose dopamine did not prevent, but delayed and attenuated, the reduction in intestinal mucosal blood flow during normotensive endotoxaemia and exerted vasodilatator properties in the villus microcirculation.

References

1. Berg RD. Translocation of indigenous bacteria from the intestinal tract. In: Hentges DJ, ed. *Human Intestinal Microflora in Health and Disease.* Orlando: Academic Press Inc, 1983; 333–352.
2. O'Dwyer ST, Mitchie HR, Ziegler TR, Revhaug A, Smith RJ, Wilmore DW. A single dose of endotoxin increases intestinal permeability in healthy humans. *Archives of Surgery* 1988; **123**: 1459–1464.
3. Jennings G, Lunn PG, Elia M. The effect of endotoxin on gastrointestinal transit time and intestinal permeability. *Clinical Nutrition* 1995; **14**: 35–41.
4. Deitch EA, Specian RD, Berg RD. Endotoxin-induced bacterial translocation and mucosal permeability: Role of xanthine oxidase, complement activation and macrophage products. *Critical Care Medicine* 1991; **19**: 785–791.
5. Deitch EA, Kemper AC, Specian RD, Berg RD. A study of the relationship among survival, gut-origin sepsis, and bacterial translocation in a model of systemic inflammation. *Journal of Trauma* 1992; **32**: 141–147.
6. Deitch EA. The role of intestinal barrier failure and bacterial translocation in the development of systemic infection and multiple organ failure. *Archives of Surgery* 1990; **125**: 403–404.
7. Fink MP, Antonsson JB, Wang H, Rothschild HR. Increased intestinal permeability in endotoxic pigs. Mesenteric hypoperfusion as an etiologic factor. *Archives of Surgery* 1991; **126**: 211–218.
8. Xu D, Qi Lu, Guillory D, Cruz N, Berg R, Deitch EA. Mechanisms of endotoxin-induced intestinal injury in a hyperdynamic model of sepsis. *Journal of Trauma* 1993; **34**: 676–683.
9. Fink MP, Kaups KL, Wang H, Rothschild HR. Maintenance of superior mesenteric artery perfusion prevents increased intestinal mucosal permeability in endotoxic pigs. *Surgery* 1991; **110**: 154–161.
10. D'Orio V, El Allaf D, Juchmes J, Marcelle R. The use of low doses of dopamine in intensive care medicine. *Archives Internationales de Physiologie et de Biochimie* 1984; **92**: S11–S20.
11. Hayakawa J, Itoh T, Kanemura K, Shibataa T, Usuda Y. Effect of dopamine and prostaglandin E1 on portal venous oxygenation. *Masui* 1994; **43**: 684–688.
12. Segal JM, Phang PT, Walley KR. Low-dose dopamine hastens onset of gut ischemia in a porcine model of hemorrhagic shock. *Journal of Applied Physiology* 1992; **73**: 1159–1164.
13. Gore RW, Bohlen HG. Microvascular pressures in rat intestinal muscle and mucosal villi. *American Journal of Physiology* 1977; **233**: H685–693.
14. Bohlen HG, Gore RW. Preparation of rat intestinal muscle and mucosa for quantitative microcirculatory studies. *Microvascular Research* 1976; **11**: 103–110.
15. Butcher EC, Weissmann IL. Direct fluorescent labelling of cells with fluorescein or rhodamin isocyanate. I. Technical aspects. *Journal of Immunological Methods* 1980; **37**: 97–108.
16. Sarelius IH, Duling BR. Direct measurement of microvessel hematocrit, red cell flux, velocity and transit time. *American Journal of Physiology* 1982; **243**: H1018–1026.
17. Mithöfer K, Schmidt J, Gebhard MM, Buhr HJ, Herfarth C, Klar E. Measurement of blood flow in pancreatic exchange capillaries with FITC-labeled erythrocytes. *Microvascular Research* 1995; **49**: 33–48.
18. Chun K, Drugas D, Biewer J, Clemens MG. Intestinal villus microcirculatory response to hemorrhage in adult and in immature rats. *Journal of Pediatric Surgery* 1992; **27**: 322–328.
19. Barbee JH, Cokelet GR. The Fahraeus effect. *Microvascular Research* 1971; **3**: 6–16.
20. Albrecht KH, Gaehtgens P, Pries A, Heuser M. The Fahraeus effect in narrow capillaries (i.d. 3.3 to 11.0 μm). *Microvascular Research* 1979; **18**: 33–47.
21. Theuer CJ, Wilson MA, Steeb GD, Garrison RN. Microvascular constriction and mucosal hypoperfusion of the rat small intestine during bacteremia. *Circulatory Shock* 1993; **40**: 61–68.
22. Spain DA, Wilson MA, Bar-Natan MF, Garrison RN. Nitric oxide synthase inhibition aggravates intestinal microvascular vasoconstriction and hypoperfusion of bacteremia. *Journal of Trauma* 1994; **36**: 720–725.
23. Deitch EA, Berg R, Specian R. Endotoxin promotes the translocation of bacteria from the gut. *Archives of Surgery* 1987; **122**: 185–190.
24. Reilly PM, Bulkley GB. Vasoactive mediators and splanchnic perfusion. *Critical Care Medicine* 1993; **21**: 55–68.
25. Lundgren O, Haglund U. The pathophysiology of the intestinal countercurrent exchanges. *Life Sciences* 1978; **23**: 1411–1422.
26. Bohlen HG. Intestinal tissue pO_2 and microvascular responses during glucose exposure. *American Journal of Physiology* 1980; **238**: H164–H171.
27. Shepherd AP, Kiel JW. A model of countercurrent shunting of oxygen in the intestinal villus. *American Journal of Physiology* 1992; **262**: H1136–1142.
28. Granger DN, Valleau JD, Parker RE, Lane RS, Taylor AE. Effects of adenosine on intestinal hemodynamics, oxygen delivery, and capillary fluid exchange. *American Journal of Physiology* 1978; **235**: H707–H719.
29. Falk A, Redfors S, Myrvold H, Haglund U. Small intestine mucosal lesions in feline septic shock: a study on the pathogenesis. *Circulatory Shock* 1985; **17**: 327–337.
30. Bulkley GB, Kvietys PR, Parks DA, Perry MA, Granger DN. Relationship of blood flow and oxygen consumption to ischemic injury in the canine small intestine. *Gastroenterology* 1985; **89**: 852–857.
31. Gutierrez G, Palizaz F, Doglio G, Wainsztein N, Gallesio A, Pacin J, Dubin A, Schiavi E, Jorge M, Pusajo J, Klein F, San

Roman E, Dorfman B, Shottlender J, Giniger R. Gastric mucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet* 1992; **339**: 195–199.

32. Kulka PJ, Tryba M. Inotropic support of the critically ill patient. A review of the agents. *Drugs* 1993; 45: 654–667.
33. Johnson DJ, Johannigman JA, Branson RD, Davis K, Hurst JM. The effect of low dose dopamine on gut hemodynamics during PEEP ventilation for acute lung injury. *Journal of Surgical Research* 1991; 50: 344–349.
34. Sakio H, Ohtsu S, Okuda C. How should we treat intestinal ischemia? 1. Effects of dobutamine and dopamine. *Masui* 1994; **43**: 1304–1309.
35. Pawlik W, Mailman D, Shanbour LL, Jacobson ED. Dopamine effects on the intestinal circulation. *American Heart Journal* 1976; **91**: 325–331.
36. Amenta F, Collier WL, Ricci A. Autoradiographic localization of vascular dopamine receptors. *American Journal of Hypertension* 1990; **3**: 34S–36S.

British Journal of Anaesthesia 1996; 76: 713–720

Early effects of total hepatectomy on haemodynamic state and organ uptake of catecholamines in the pig

M. F. M. JAMES, R. HICKMAN, P. JANICKI, B. METS AND J. FOURIE

Summary

In a previous study, we showed that plasma concentrations of catecholamines were increased during the anhepatic phase in pigs. In this study, we investigated if a constant depth of anaesthesia would prevent these changes and, if not, if the changes were caused by impaired extraction of catecholamines. We measured arterial and venous pressures, heart rate and cardiac output in 10 anaesthetized pigs. Hepatic arterial and portal venous flows were measured. Blood for measurement of catecholamines was sampled from carotid and pulmonary arteries and portal, hepatic and renal veins. After a 2-h observation period, the liver was removed and the circulation reconstituted. Measurements were made and samples obtained for another 2 h. Catecholamine concentrations increased 2–10-fold after hepatectomy. Before hepatectomy, noradrenaline was extracted by the lung (mean extraction ratio 23 (SEM 8)%) and the liver (30 (11)%); after hepatectomy, there was extraction by the kidney (24 (12)%) but extraction by the lung (29 (8)%) was unchanged. Before hepatectomy, adrenaline was extracted predominantly by the kidney (73 (5)%) and the liver (70 (6)%), with minimal extraction by the lung; after hepatectomy, extraction by the lung increased (25 (4)%) and decreased slightly in the kidney (56 (6)%). While mean arterial pressure did not change, heart rate increased by approximately 50% and cardiac index declined (ns) within 2 h after hepatectomy. There was a sharp increase in pulmonary vascular resistance after removal of the liver and changes correlated with increases in arterial plasma concentrations of catecholamines. (*Br. J. Anaesth.* 1996; **76**: 713–720)

Key words

Liver, failure. Surgery, hepatic. Sympathetic nervous system, catecholamines. Pig.

Prolonged anhepatic periods of up to 24 h have recently been suggested in patients with fulminant liver failure in order to stabilize biochemical and coagulation abnormalities [1]. Previous reports of the effects of total hepatectomy in animals were discouraging because of numerous complications, and thus in an earlier study we made a preliminary investigation of some of the early effects of total hepatectomy [2]. In that study, we observed a marked increase in plasma concentrations of noradrenaline and adrenaline but it was unclear if the changes were caused by the absence of the liver, or to surgical stimulation and possibly associated haemodynamic changes. In that study the anaesthetic technique was not strictly controlled and haemodynamic or respiratory monitoring was not performed. In this study, a constant partial pressure of inspired anaesthetic gas was maintained, and haemodynamic changes, including blood flow to the liver and lung were monitored carefully. Detailed haemodynamic monitoring was used so that fluid balance could be corrected against measured right and left ventricular preload, and also to allow analysis of the haemodynamic consequences of catecholamine changes. The effects of surgical removal of the liver and the subsequent stabilization period were compared with results obtained during the preceding period of liver mobilization and placement of monitoring devices and the subsequent stabilization period. Blood samples for measurement of catecholamines were obtained across the liver, lung and kidney in order to determine net flux across these organs. Trans-organ extraction of catecholamines was studied in order to assess the extent to which removal of the liver contributed to the previously observed increase in catecholamine concentrations.

Materials and methods

The study was approved by the Animal Research Ethics Committee of the University of Cape Town. We used 10 young Large White Landrace pigs, weighing 23–29 kg (mean 25 (SEM 1) kg) and aged 7–9 weeks. After a fasting period of 16 h, anaesthesia was induced with sodium thiopentone 500–750 mg i.v. and pancuronium 6 mg. The trachea was intubated, a large gauge orogastric tube was passed

---

M. F. M. JAMES‡, MB, CHB, PHD, FRCA, P. JANICKI*, MD, PHD, B. METS†, MB, CHB, PHD, FFA(SA) (Department of Anaesthesia); JOAN FOURIE, PHD (Department of Surgery); ROSEMARY HICKMAN, CHM, MD (MRC Liver Centre); University of Cape Town, South Africa. Accepted for publication: January 5, 1996.

Present addresses:

*Department of Anesthesiology, Vanderbilt University, Nashville, TN, USA.

†Department of Anesthesiology, College of Physicians and Surgeons of Columbia University, New York, NY, USA.

‡Address for correspondence: Department of Anaesthesia, University of Cape Town Medical School, Observatory, Western Cape 7925, South Africa.

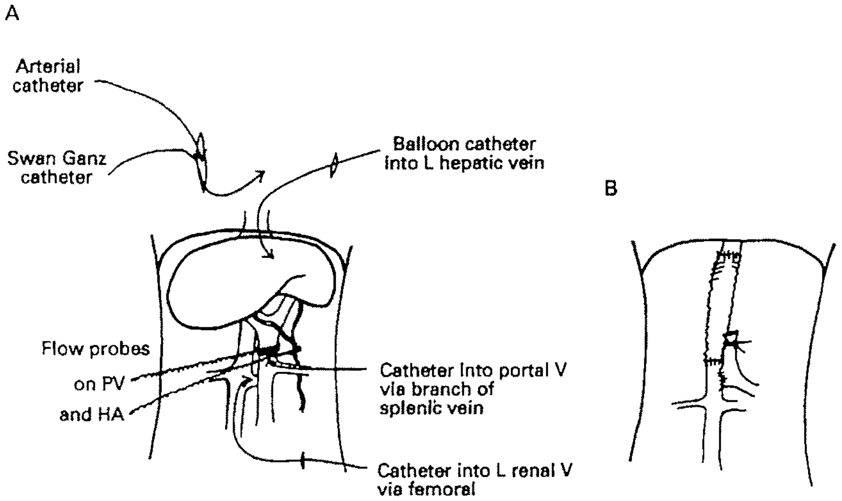

A
Arterial catheter
Swan Ganz catheter
Balloon catheter into L hepatic vein
B
Flow probes on PV and HA
Catheter into portal V via branch of splenic vein
Catheter into L renal V via femoral

Figure 1 A: Schematic diagram of the positions of all catheters and flow probes in animals before hepatectomy. B: Schematic diagram of the completed surgical model showing interposition of the Dacron vascular graft between the supra- and infrahepatic venae cavae. PV = Portal vein, HA = hepatic artery, V = vein, L = left.

and the animals transferred immediately to the operating room while the lungs were ventilated manually. In the operating room anaesthesia was maintained with isoflurane 1.5 kPa and 66 % nitrous oxide in oxygen, delivered from a temperature compensated isoflurane vaporizer (Tec Mark IV, Ohmeda, UK), the accuracy of which had been pre-checked. The lungs were ventilated mechanically using a circle system with carbon dioxide absorption. Normocapnia was monitored by arterial blood-gas analysis and capnography.

POSITIONING OF CATHETERS AND FLOW PROBES (FIG. 1)

On the right side of the neck, size 8-French gauge catheters were introduced into the common carotid artery for monitoring arterial pressure and for blood sampling, and the external jugular vein for infusion of fluid; a 7-French gauge pulmonary artery catheter was floated into the pulmonary artery. Its position was confirmed by characteristic changes in the transduced pressure waveform. Care was taken to ensure that the proximal injection port was beyond the end of the sheath introducer which had been shortened to 9 cm in length. This length had been determined by prior post-mortem dissection of comparable pigs used for other studies.

A midline incision was made from the xiphisternum to the pubis and the bowel enclosed in a large plastic bag to provide exposure and prevent evaporative fluid loss. The ligaments attaching the liver to the diaphragm were divided. Through a left neck incision, a balloon-tipped catheter was advanced via the internal jugular vein into the suprahepatic vena cava and then guided manually into the left lobe of the liver. Within the abdomen, a fine catheter (5-French gauge feeding tube) was advanced via a branch of the splenic vein to lie opposite the outflow of the pancreaticoduodenal vein. Via a groin incision, a catheter (8-French gauge feeding tube) was introduced into the femoral vein and manipulated 10–15 mm into the right renal vein. These are modifications of techniques described previously [3]. The portal vein from the porta hepatis caudad to the confluence of the splenic and mesenteric veins and the common hepatic artery to the same level were dissected free of surrounding tissue and lymph nodes. Pre-calibrated perivascular ultrasonic flow cuffs were placed around the hepatic artery (2 mm) and the portal vein (6 mm), and positioned to ensure measurement of total flow in each vessel using an ultrasonic flowmeter (Transonic Systems Inc., New York, NY, USA, Model T201D) which incorporates a non-occlusive zero facility. The abdomen was closed loosely and observations made, during this pre-hepatectomy phase, immediately after surgery and at hourly intervals over the next 2 h.

I.v. balanced electrolyte solution (Plasmalyte B, Baxter, South Africa) with added 2.5 % glucose was infused at a rate of 10 ml kg^{-1} h^{-1} using a constant infusion pump. This solution resembles lactated Ringer's solution with the exception that the lactate is replaced by bicarbonate, and calcium is excluded. An infusion of 4.2 % sodium bicarbonate 150 ml was given during the period of bypass. Additional fluid was infused through the sheath introducer as needed to maintain a constant pulmonary artery wedge pressure.

Cardiac output and core temperature were measured using a cardiac output monitor (9520A; Edwards Laboratories, CA, USA). Cardiac output measurements in triplicate were performed by injection of 5 ml of normal saline (< 5 °C). Injections were made by a single investigator over a period of less than 4 s at end-expiration.

At the end of the initial observation period, hepatectomy was performed using a modification of previous methods [2]. The abdomen was re-opened and a side-to-side portacaval shunt was established just cephalad to the renal veins and the junction of the splenic and mesenteric veins, using 5-0 non-absorbable sutures. A passive porto-systemic shunt was produced by inserting catheters (22-French gauge) into the splenic vein and the left external jugular vein. For hepatectomy, the infrahepatic vena cava was clamped and the caudal end of the vena cava sutured to one end of a Dacron aortic graft (diameter 12–14 mm). During this time the vena caval and portal circulations passed through the portal vein and the passive bypass. After completion of this anastomosis, the liver was removed definitively and the anastomosis between the suprahepatic vena cava and the end of the graft completed. During this time, the vena caval and portal flows were decompressed partially via the passive shunt. After expulsion of air from the Dacron graft, the clamps were removed and circulation was restored. Total portal and vena caval flow now passed through the graft. The passive shunt was then removed and the orifice in the splenic vein repaired. The abdomen was closed with chromic catgut and nylon sutures. Measurements were made immediately after total hepatectomy and at hourly intervals for the next 2 h.

Blood samples were analysed for acid–base status, Pa_{O_2}, Pa_{CO_2}, and plasma sodium, potassium and lactate concentrations. Plasma concentrations of catecholamines were measured by high pressure liquid chromatography with electrochemical detection using dehydrobenzylamine as the internal standard. The coefficient of variation was 7.9 % for noradrenaline and 8.7 % for adrenaline, and the limit of sensitivity was 10 pg ml^{-1}. Catecholamine extraction ratios (ER) were calculated for the lung, kidney, gut and spleen as:

$$\mathrm{ER} = \frac{(\text{arterial concentration} - \text{venous concentration})}{\text{arterial concentration}} \times 100$$

For the lung, pulmonary venous concentration was assumed to be the same as systemic arterial concentration. For the liver, the formula was:

$$\mathrm{ER} = \frac{(\text{PVconcn} \times \text{PV flow}) + (\text{HAconcn} \times \text{HA flow}) - (\text{HVconcn} \times \text{total flow})}{(\text{PVconcn} \times \text{PVflow}) + (\text{HAconcn} \times \text{HA flow})} \times 100$$

where PV = portal vein, HA = hepatic artery, HV = hepatic vein and concn = concentration.

The total mass of catecholamines extracted by the pulmonary vascular bed and by the liver at each time was obtained by multiplying the difference between inflow and outflow concentration by total organ flow at each time. This was not possible for other organ beds as flow across them was not measured.

Statistical evaluation was performed using Statgraphics (version 5) statistical package on an IBM compatible 386 PC running under MS DOS version 6. All comparisons were against preoperative values unless otherwise stated. Extraction ratios were compared before and after hepatectomy using the paired *t* test. Time-based changes in catecholamine concentrations, extraction ratios, biochemical data and cardiovascular variables were analysed using analysis of variance for repeated measures with individual significantly different groups identified using the 95 % confidence interval multiple range testing method. Changes in haemodynamic variables were compared with changes in catecholamine concentrations in the appropriate vascular bed by regression analysis. Non-normally distributed variables were compared using the Mann-Whitney *U* test. Results are reported as mean (SEM).

Results

The mean time for porto-caval shunt, removal of the liver and replacement with the Dacron graft was 26 (SEM 4) min and the period of portal venous bypass never exceed 11 min. During the 5 h of the procedure, a mean of 2054 (450) ml of fluid were infused i.v. (range 1700–2700 ml). All pigs required additional fluids in excess of 10 ml kg^{-1} h^{-1} to maintain a constant wedge pressure. The mean additional fluid requirement was 33 (5.7) ml kg^{-1} over the 5 h of the procedure, and thus each pig received a mean of 15.8 (1) ml kg^{-1} h^{-1} throughout the experiment. It was noted that the pigs sequestered considerable quantities of fluid into the peritoneal cavity during the study and it was thought that this accounted for the additional fluid requirements. One pig died after hepatectomy.

HAEMODYNAMIC VARIABLES (FIG. 2)

Mean arterial pressure did not change significantly throughout each phase of the experiment. Initial heart rate was 135 (7) beat min^{-1} and increased to 161 (13) beat min^{-1} (ns) during the pre-hepatectomy phase. Two hours after removal of the liver, heart rate reached 184 (11) beat min^{-1} after 2 h ($P < 0.05$ compared with baseline). Cardiac index, expressed as a function of body weight, was 0.120 (0.011) litre kg^{-1} min^{-1} at the start of the study and decreased to 0.079 (0.014) litre kg^{-1} min^{-1} at the end of the study (ns). Weight rather than body surface area (BSA) was used to express cardiac index, as there are no nomograms for BSA in pigs. Pulmonary capillary

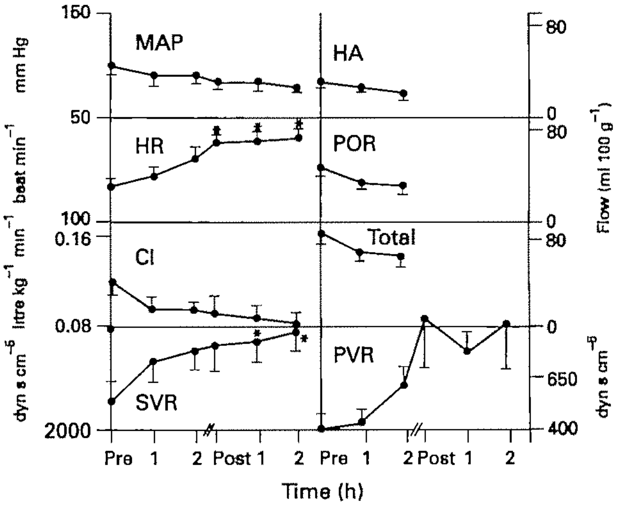


Figure 2 Mean arterial pressure (MAP), heart rate (HR), cardiac index (CI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), hepatic arterial (HA), portal (POR) and total liver blood flows (mean, SEM). Measurements were made after positioning of all catheters and flow probes (Pre) and 1 and 2 h thereafter, and again immediately after removal of the liver and restoration of all circulations (Pre) and 1 and 2 h thereafter. * $P < 0.05$ between pre- and post-hepatectomy data.

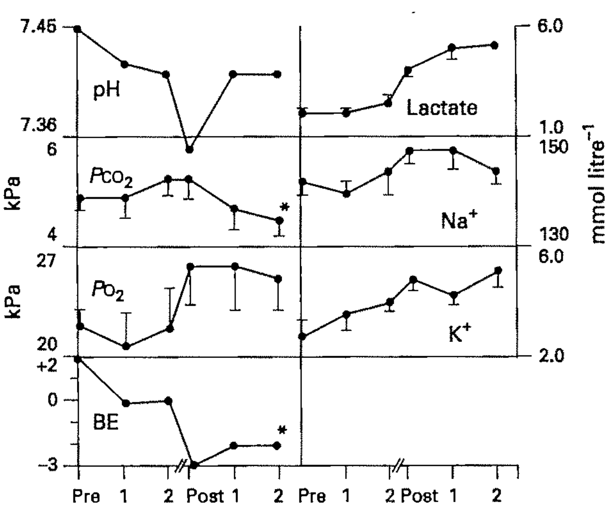


Figure 3 Plasma pH, $P\text{CO}_2$, $P\text{O}_2$, base excess (BE), and lactate, sodium (NA^+) and potassium (K^+) concentrations in arterial blood obtained at intervals described in figure 2. Error bars are not shown for pH or BE as they were too small for accurate depiction. $*P < 0.05$ between pre- and post-hepatectomy data.

wedge pressure was 6 (1) mm Hg and pulmonary arterial pressure was 20 (7) mm Hg at the beginning of the study. These values were not significantly different from values 2 h after hepatectomy (5 (1) mm Hg and 20 (9) mm Hg, respectively). Computation of systemic vascular resistance showed this to be 2378 (321) dyn s cm^{-5} at the beginning and 3473 (341) dyn s cm^{-5} at the end of the study, while pulmonary vascular resistance (PVR) increased slowly from 404 (72) to 630 (82) dyns cm^{-5} (ns) at the end of the pre-hepatectomy phase. There was a sharp 2–4-fold increase in PVR (mean 920 (231) dyn s cm^{-5}) in all animals immediately after removal of the liver which persisted for 2 h after hepatectomy. This was significantly greater than baseline but not significant compared with values immediately before hepatectomy. Changes in PVR correlated well with noradrenaline ($r = 0.73$) and adrenaline ($r = 0.72$) concentrations in the pulmonary artery. None of the other cardiovascular variables correlated significantly with changes in catecholamine concentrations.

All aspects of liver blood flow decreased during the first 2 h of the sham operation but this was not statistically significant. Mean total liver blood flow expressed per liver weight was 90 (8) ml 100 g^{-1} at the beginning of the study which decreased to 68 (9) ml 100 g^{-1} (ns) just before removal of the liver; mean initial portal flow was 49 (5) ml 100 g^{-1} which decreased to 38 (6) ml 100 g^{-1}, while hepatic arterial flow was 37 (3) ml 100 g^{-1} at the beginning of the study and decreased to 25 (5) ml 100 g^{-1} (ns).

BIOCHEMISTRY (FIG. 3)

There was a sharp decrease in plasma pH immediately after removal of the liver but otherwise pH values remained within normal limits. Mean initial Pa_{CO_2} was 4.9 (0.5) kPa which remained unaltered until the first hour after removal of the liver when a decrease was noted which became significant by 2 h after hepatectomy (4.2 (0.4) kPa). Plasma base excess declined from +2 to 0 mmol litre^{-1} before hepatectomy to −3 mmol litre^{-1} immediately and for 2 h after removal of the liver. There was an apparent increase in Pa_{O_2} after hepatectomy (ns).

While mean plasma concentrations of sodium were unaltered during the study, there was a slow increase in plasma potassium from 3.4 (0.3) to 4.6 (0.3) mmol litre^{-1}, 2 h after removal of the liver. There was a sustained but non-significant increase in mean plasma lactate concentrations after removal of the liver from 2–3 to 4–6 mmol litre^{-1}.

ABSOLUTE CATECHOLAMINE CONCENTRATIONS (TABLE 1)

Noradrenaline concentrations remained within the normal range for our laboratory (235–320 pg ml^{-1}) at all sites during the control period. Immediately after removal of the liver, there was a significant 5–10-fold increase in noradrenaline concentrations at all sites. One hour after hepatectomy, all concentrations decreased, with significant reductions from the previous sample in the arterial and renal vein samples. By 2 h after hepatectomy, all concentrations were increased significantly.

Table 1 Absolute catecholamine concentrations (mean (SEM) pg ml^{-1}) in various circulations at the following sampling times: immediately after catheterization (i), 1 h (ii) and 2 h (iii) thereafter; immediately after total hepatectomy and restoration of the circulation (iv), 1 h (v) and 2 h (vi) thereafter. a = Artery, v = vein. $*P < 0.05$ compared with (i)–(iii) inclusive; $\dagger P < 0.05$ compared with (i); $\ddagger P < 0.05$ compared with (iv) and (v); $\S P < 0.05$ compared with all except (iv)

	Time					
	(i)	(ii)	(iii)	(iv)	(v)	(vi)
Noradrenaline						
Arterial	220 (38)	300 (112)	380 (110)	1980 (818*)	858 (187)‡	1060 (245)†
Portal v	215 (44)	335 (82)	330 (107)			
Hepatic v	182 (53)	140 (55)	263 (46)			
Renal v	182 (41)	268 (80)	420 (101)	1208 (425)*	391 (125)‡	719 (161)*
Pulmonary a	403 (119)	440 (162)	506 (177)	2400 (927)*	1080 (178)	1839 (521)*
Adrenaline						
Arterial	160 (36)	239 (87)	210 (53)	1008 (380)	400 (146)	1100 (416)
Portal v	80 (18)	130 (31)	100 (30)			
Hepatic v	64 (13)	56 (13)	58 (15)			
Renal v	50 (16)	80 (13)	70 (19)	295 (122)	113 (35)	267 (141)
Pulmonary a	240 (68)	340 (112)	271 (78)	1256 (411)	480 (161)	840 (257)

Table 2 Catecholamine extraction ratio (mean (SEM) %) in various circulations at the following sampling times: immediately after catheterization (i), 1 h (ii) and 2 h (iii) thereafter; immediately after total hepatectomy and restoration of the circulation (iv), 1 h (v) and 2 h (vi) thereafter. $*P < 0.05$, $***P < 0.001$ compared with zero

	Pre-hepatectomy ($n = 10$)				Post-hepatectomy ($n = 9$)			
	(i)	(ii)	(iii)	Mean (i–iii)	(iv)	(v)	(vi)	Mean (iv–vi)
Noradrenaline								
Pulmonary	16 (9)	29 (6)*	24 (10)*	23.3 (8.1)*	23 (5)*	24 (10)*	39 (6)*	28.6 (8.0)*
Renal	4 (14)	2 (18)	−14 (16)	−0.1 (0.2)	22 (12)	35 (8)*	15 (7)	23.6 (12.3)*
Hepatic	19 (21)	55 (14)	18 (23)	30.7 (11.8)*				
Splanchnic	−16 (10)	−14 (8)	−56 (32)	−28.2 (21.7)				
Adrenaline								
Pulmonary	8 (12)	10 (8)	15 (7)	10.9 (5.2)	21 (8)***	32 (7)***	22 (12)*	26.7 (5.9)***
Renal	74 (6)***	70 (8)***	76 (5)***	73.2 (3.5)***	70 (4)***	48 (12)***	52 (9)***	56.2 (5.9)***
Hepatic	55 (8)***	76 (6)***	80 (8)***	70.2 (4.6)***				
Splanchnic	40 (12)*	52 (8)*	54 (12)*	48.3 (6.7)*				

Table 3 Total mass of catecholamines (mean (SEM)) extracted from the pulmonary and hepatic circulations at each time; immediately after catheterization (i), 1 h (ii) and 2 h (iii) thereafter; immediately after total hepatectomy and restoration of the circulation (iv), 1 h (v) and 2 h (vi) thereafter

	Noradrenaline		Adrenaline	
Sample No.	Hepatic extraction (ng)	Pulmonary extraction (ng)	Hepatic extraction (ng)	Pulmonary extraction (ng)
(i)	5.03 (37.6)	227.25 (42.3)	99.21 (39.7)	147.97 (67.4)
(ii)	81.48 (38.0)	334.99 (128.1)	95.90 (40.8)	203.91 (164.3)
(iii)	54.23 (32.1)	320.98 (171.9)	68.04 (32.1)	114.92 (58.8)
(iv)		690.29 (162.8)		338.99 (99.7)
(v)		1072.80 (146.9)		195.52 (61.2)
(vi)		1393.86 (409.8)		318.26 (172.9)

Concentrations of adrenaline in samples before hepatectomy were unchanged during the control period. After removal of the liver, there was an increase of up to six-fold above baseline in arterial and pulmonary arterial samples but not in those from the renal vein. There was a non-significant decrease 1 h after hepatectomy; at 2 h, concentrations in all circulations were significantly greater than pre-hepatectomy values.

TRANS-ORGAN CATECHOLAMINE CONCENTRATIONS

The majority of individual trans-organ samples showed reductions in effluent catecholamine concentrations (extraction) across individual organs, although there were several samples in which net release of catecholamines occurred.

Pulmonary extraction of catecholamines

Extraction of noradrenaline occurred across the lung in all but seven of the samples, both before and after hepatectomy, and significant noradrenaline extraction was demonstrated at all but one time (table 2). Mean extraction of noradrenaline across the lung was significantly different from zero for both pre- and post-hepatectomy samples ($P < 0.05$). One-third of specimens showed release of adrenaline across the pulmonary circulation during the pre-hepatectomy phase, but only one sample showed release after hepatectomy. However, the mean extraction ratio at each time was always positive (table 2), although not significantly different from zero. Averaged over the three sampling intervals after hepatectomy, the mean extraction ratio was significantly different from zero. After hepatectomy, the total mass of noradrenaline extracted by the pulmonary bed increased 2–4 fold from pre-hepatectomy concentration whereas that of adrenaline increased only 1–2 fold (table 3)

Hepatic extraction of catecholamines

Noradrenaline extraction varied before hepatectomy and only six samples showed release. Overall, there was a mean extraction of noradrenaline which was significantly different from zero ($P < 0.05$) during the pre-hepatectomy period (table 2). Only one sample showed release of adrenaline in the pre-hepatectomy phase and there was a consistently high extraction ratio (table 2). The overall mean extraction of adrenaline by the liver was 66.7 (6.2) %. Despite this high (statistically significant) extraction, the total mass of both catecholamines extracted by the liver was less than that extracted by the lung before hepatectomy (table 3). After hepatectomy the mass of both catecholamines extracted by the lung exceeded that of both the lung and liver combined, before removal of the liver for all times except for adrenaline at time (v) (table 3).

Renal extraction of catecholamines

In the pre-hepatectomy phase, only two-thirds of samples showed extraction of noradrenaline. Consequently, there was no significant net uptake or release of noradrenaline during this period. After removal of the liver only seven of 30 samples showed release of noradrenaline. There was a very high extraction of adrenaline during the pre-hepatectomy phase which persisted at the first sampling interval after removal of the liver but declined thereafter. Only one sample in the entire study showed release, and the concentration of adrenaline released in that sample was at a level within the experimental error.

Gut and splenic (splanchnic) extraction of catecholamines

There was an overall release of noradrenaline from the gut and spleen before hepatectomy but this was not statistically significant. There was significant mean extraction of adrenaline by this vascular bed.

Discussion

This study follows the suggestion of Ringe, Pichlmayr and Luebbe [1] that appropriate liver transplant recipients may be subjected to a prolonged anhepatic phase to allow stabilization of the haemodynamic and biochemical state. Previous studies of anhepatic animals have however, suggested that there may be severe consequences of total removal of the liver, but many of these changes were probably related to the models used [4]. In earlier study, a more stable anhepatic model in the pig was described which would survive at least 12 h and occasionally up to 24 h [2]. In this study, special attempts were made to maintain animals in a steady state. The only significant changes in biochemical measurements were plasma potassium and lactate concentrations. The two-fold increase in mean plasma lactate concentrations was consistent with the findings of Ringe, Pichlmayr and Luebbe who reported a 6–8-fold increase 8 h after hepatectomy in their clinical study of liver transplant recipients [1].

Particular attention was paid in this study to plasma catecholamine concentrations because these had not been measured previously during the anhepatic state in normal animals and because they may have significant early effects on the liver transplant recipient during revascularization of the graft. Catecholamine concentrations increased significantly in all circulations after hepatectomy and the question arises if this was a result of diminished extraction or increased release. Several authors believe that the liver is the major contributor to catecholamine extraction and there are various reports of a clearance ratio of 0.9 [5, 6], an extraction ratio of 62 (5 %) for the hepaticomesenteric sequence [7], clearance by the liver at levels increased fourfold by exogenous administration of catecholamines [8] and significant preferential clearance of noradrenaline by the liver [9] with net removal despite increased sympathetic activity [8]. Korn, Waldhaust and Iratusch-Marrain suggested that the magnitude of hepatic removal correlates with hepatic blood flow [10] although there was no correlation between liver blood flow and extraction ratios in our study. Hepatic removal of catecholamines probably buffers the net release of noradrenaline by the hepatomesenteric sequence, but this effect is seen only in studies in which both portal and hepatic venous blood is sampled [11]. The role of the liver in the removal of catecholamines is also implied in patients with cirrhotic liver disease who manifest very high circulating concentrations, but Silverberg, Shah and Maymond commented that, although it occurs, hepatic inactivation of noradrenaline is only a fraction of the systemic clearance in normal subjects [12].

Our data confirm an important role for the liver in catecholamine extraction, but also show that the lung is a more important site for catecholamine removal. Our results are in agreement with the 25 % pulmonary extraction of noradrenaline reported by Sole and colleagues [13]. Despite the lower extraction ratio for both catecholamines, the lung assumes a major role in catecholamine extraction because the entire circulating blood volume passes through this capillary bed. In the absence of the liver, the mass of catecholamines extracted by the lung more than compensated for the loss of hepatic metabolism.

There appear to be considerable disagreement about the role of the kidney in catecholamine extraction. Release of noradrenaline into the renal circulation has been reported in humans [14] and Oliver and colleagues found that in dogs there was basal release and a correlation between plasma concentrations of noradrenaline and stimulated sympathetic activity [15]. In a recent study, net removal of noradrenaline by the kidney was demonstrated at plasma concentrations midway between our pre- and post-hepatectomy levels [11]. Ring Larsen and colleagues, studying patients with cirrhosis, suggested that increased sympathetic activity in the kidney may be in response to hypotension or decreased peripheral resistance [14] although we did not find evidence of this. Others have reported that extraction occurs after injection of exogenous catecholamines. In this study, adrenaline extraction by the kidney was consistently high, whereas both extraction and release of noradrenaline occurred, which agrees with previous findings [14]. Extraction of adrenaline may, however, be a saturable mechanism, in view of the decrease in the extraction ratio which occurred after the marked increase in adrenaline after hepatic removal. It should be noted that, on the presumption that renal blood flow remained a reasonably constant fraction of cardiac output, the mass of catecholamines extracted by the kidney was probably greatly increased at this time.

The role played by the gut and spleen has only recently been considered [11, 16]. Although many studies have reported on the splanchnic or hepatomesenteric circulations [9, 10, 13, 17] in only one of these studies were transhepatic measurements made [10]. Our data showed equal release or uptake of noradrenaline by the gut and spleen and significant uptake of adrenaline, but studies were not continued after removal of the liver. Preliminary results from further studies suggest that catecholamine release is from the gut, and that the spleen plays little part [unpublished data].

There appear to be very few reports of the influence of anaesthetic technique on haemodynamic monitoring in normal pigs, although Weiskopf and colleagues have published the effects of ketamine and thiopentone [18] or nitrous oxide and halothane [19] in hypovolaemic swine. The initial increase in catecholamine concentrations after hepatic resection could have been in response to the surgical procedure, although the partial pressure of isoflurane with 70% nitrous oxide (equivalent to 2 MAC in humans) should have been sufficient to control autonomic responses. This is supported by the fact that the initial surgical procedure, which should have been at least as stimulating as hepatectomy, particularly as it involved skin incision, resulted in catecholamine concentrations within the normal ranges for pigs in our laboratory and no cardiovascular evidence of sympathetic response. The chosen regimen resulted in a moderately stable state with no significant changes in mean arterial pressure, heart rate, cardiac output and pulmonary or systemic vascular resistance during the first 2 h before hepatectomy. However, heart rate increased gradually throughout the study, and was significantly higher than baseline after hepatectomy, although there was no significant increase from the immediate pre-hepatectomy rate. Subsequent experience with the model has suggested that pigs may require even larger fluid loads than those given in this experiment to maintain intravascular volumes in the face of considerable transudation into the peritoneal cavity. Although pulmonary artery wedge pressure was maintained reasonably constant throughout the experiment, it is possible that the increase in heart rate was because of a relative fluid deficit which was not detected by measurements of wedge pressure alone.

The development of increased pulmonary vascular resistance in the anhepatic and revascularization phases of liver transplantation has been noted previously [unpublished clinical and laboratory observations]. It has been postulated that these changes are related to increased circulating endotoxins, prostaglandins or substance P [20] resulting from the anhepatic state, but increased catecholamine concentrations may also play a role. Our animals were not anticoagulated during the brief period of portal venous bypass, and it is possible that there may have been some clot formation in the graft with pulmonary embolization, although there was no gross evidence of this in terms of occlusion of the bypass catheter. However, the fact that pulmonary vascular resistance correlated well with pulmonary arterial catecholamine concentrations suggests that this observation in the present study was probably a result of the increase in catecholamine concentration or some other simultaneous and parallel event such as an increase in circulating endotoxin. This response of the pulmonary vasculature may be a species-specific effect. Kogure and Suzuki [21] demonstrated an increase in plasma histamine concentrations in portal venous blood after hepatic inflow occlusion. We did not measure histamine concentrations, and this may be an alternative explanation for the increase in pulmonary vascular resistance.

Partial disruption of the circulation at the time of hepatectomy may also have played an important role in the high concentrations of catecholamines. This suggestion is supported by the study of Kogure and Suzuki who showed that hepatic inflow occlusion resulted in significant increases in both portal and systemic plasma concentrations of noradrenaline after 30 min of occlusion time, increasing with time, and that very high concentrations of noradrenaline were associated with poor survival [21]. As the increase was more marked in the portal rather than the systemic circulation, they attributed the increase to splanchnic congestion. In our study, decompression of the portal and vena caval systems through a single bypass was almost certainly inadequate during excision of the liver (±11 min) and some degree of portal congestion would have occurred over this period. Recent evidence of the role of the mesenteric organs in the turnover of noradrenaline supports the possibility that the splanchnic circulation may be an important source of the increased catecholamine concentrations [11, 16].

We conclude therefore that changes in plasma catecholamines and organ extraction are considerable and may be clinically relevant. If these studies are applicable to humans, it would seem likely that an increase in circulating catecholamines may occur during prolonged anhepatic states, but that this increase is not entirely a result of loss of the hepatic metabolism of catecholamines. This study does not shed light on either the source of catecholamine release in the anhepatic phase, or the stimulus which mediated the change. However, the secondary increase in catecholamine concentrations 2 h after surgical manipulation had ceased suggests that the stress of the anhepatic state is at least partially responsible for the increase. These changes may not be reproduced in cirrhotic transplant recipients who may have altered sympathetic tone and abnormal responses to catecholamines [22]. In addition, infusion of catecholamines during anaesthesia produces changes greater than those seen in these experiments. Nevertheless, it is possible that the increased catecholamine concentrations which we have demonstrated could have adverse effects on both hepatic and pulmonary blood flow when a new liver is implanted. Ongoing studies with anhepatic pigs have demonstrated marked attenuation of renal output after removal of the liver, which is probably related to the increase in catecholamine concentrations [unpublished data]. Further studies are being conducted to determine if and how rapidly revascularization of the liver reverses these changes.

References

1. Ringe B, Pichlmayr R. Luebbe N. Total hepatectomy as a temporary approach to acute hepatic or primary graft failure *Transplantation Proceedings* 1988; **10**: 552–557.
2. Hickman R, Bracher M, Tyler M, Lotz Z, Fourie J. The effect of total hepatectomy upon glucose homeostasis and coagulation in the pig. *Digestive Diseases and Science* 1992; **37**: 328–334.
3. Hickman R, Tyler M, McLeod H, Fourie J. Transhepatic sampling during experimental porcine liver autograft—its application to measurements of insulin, glucagon and glucose. *Journal of Surgical Research* 1990; **49**: 519–523.
4. Nilehn JE, Aronsen UF, Ericsson B. Changes in clotting factors after massive liver resection and total hepatectomy in dogs. *Acta Chirurgica Scandinavica* 1967; **133**: 183–188.
5. Christenssen NJ, Galbo H, Gjerus A, Henriksen JN, Kjaer

M, Ring Larsen H. Whole body and regional clearance of noradrenaline and adrenaline in man. *Acta Physiologica Scandinavica* 1984; (Suppl. 527): 17–20.

6. Henricksen JH, Ring Larsen H, Kanstrup IL, Christensen NJ. Splanchnic and renal elimination and release of catecholamines in cirrhosis. *Gut* 1984; **25**: 1034–1043.
7. Esler M, Jennings G, Leonard P, Sacharias N, Burke F, Jonas J, Blomberg P. Contribution of individual organs to total noradrenaline release in humans. *Acta Physiologica Scandinavica* 1984; (Suppl. 527): 11–16.
8. Couisineau D, Goresky CA, Rose CP. Blood flow and norepinephrine effects on liver vascular and extravascular volumes. *American Journal of Physiology* 1983; **244**: H495–504.
9. Joly JG, Leduc J, Bernier J, Lavote P, Viak C. Catecholamine levels in portal, hepatic and systemic venous blood in portal hypertension. *Lancet* 1967; **ii**: 121–123.
10. Korn A, Waldhaust W, Iratusch-Marrain P. Splanchnic exchange of catecholamines in man. *Naunyn-Schmiedebergs Archives of Pharmacology* 1980; **313**: R61.
11. Eisenhofer G, Åneman A, Hooper D, Holmes C, Goldstein DS, Friberg P. Production and metabolism of dopamine and norepinephrine in mesenteric organs and liver of swine. *American Journal of Physiology* 1995; **268**: G641–G649.
12. Silverberg AB, Shah SD, Maymond MW. Norepinephrine hormone and neurotransmitter in man. *American Journal of Physiology* 1978; **234**: E252–256.
13. Sole M, Drobac M, Schwarz L, Hussain MN, Vaughan Neil EF. The extraction of circulating catecholamines by the lungs in normal men and in patients with pulmonary hypertension. *Circulation* 1979; **60**: 160–166.
14. Ring Larsen H, Hesse B, Henriksen JH, Christensen NJ. Sympathetic nervous activity and renal and systemic hemodynamics in cirrhosis, plasma norepinephrine concentration, hepatic extraction and renal release. *Hepatology* 1982; **2**: 304–311.
15. Oliver JA, Pinto J, Sciacca RR, Cannon PJ. Basal norepinephrine overflow into the renal vein – effect of renal nerve stimulation. *American Journal of Physiology* 1980; **239**: 371–377.
16. Åneman A, Eisenhofer G, Fändriks L, Friberg P. Hepatomesenteric release and removal of norepinephrine in swine. *American Journal of Physiology* 1995; **268**: R924–R930.
17. Hazelrig CG, Zimon RP, Flock EV, Schaps SG, Schirger A, Owen CA. Role of the liver in metabolism of D-L-norepinephrine 14C. *American Journal of Physiology* 1967; **212**: 1229–1235.
18. Weiskopf RB, Bogetz MS, Roizen MF, Reid IA. Cardiovascular and metabolic sequelae of inducing anesthesia with ketamine or thiopental in hypovolemic swine. *Anesthesiology* 1984; **60**: 214–219.
19. Weiskopf RB, Bogetz MS. Cardiovascular actions of nitrous oxide versus halothane in hypovolemic swine. *Anesthesiology* 1985; **63**: 509–516.
20. Eleburg L, Wahren J, Hedenstrema G. Normalization of ventilation/perfusion relationships after liver transplantation in patients with decompensated cirrhosis. *Hepatology* 1990; **12**: 1350–1357.
21. Kogure K, Suzuki M. Effects of hepatic inflow occlusion on changes in plasma potassium, histamine and norepinephrine in rats. *Circulatory Shock* 1992; **36**: 290–298.
22. Carton EG, Rettke SR, Plevak DJ, Geiger HJ, Kranner PW, Coursin DB. Perioperative care of the liver transplant patient. Part 1. *Anaesthesia and Analgesia* 1994; **78**: 120–133.

British Journal of Anaesthesia 1996; **76**: 721–725

Sevoflurane, enflurane and isoflurane have no persistent postanaesthetic effects on the central nervous system in cats

J. KURATA, T. ADACHI, S. NAKAO, M. MURAKAWA, T. SHICHINO, M. SHIBATA AND K. MORI

Summary

Several reports have appeared on postanaesthetic convulsive disorders in humans after enflurane and isoflurane anaesthesia. However, it is controversial if enflurane induces epileptiform electroencephalogram (EEG), abnormal behaviour, or both, lasting for several days after anaesthesia in laboratory animals. We chronically implanted electrodes for EEG recording in the cortex, medial amygdala and dorsal hippocampus, and for reticular multi-unit activity (R-MUA) in the midbrain reticular formation in five cats. Two weeks later they were anaesthetized with 5.0% sevoflurane, 3.5% enflurane or 4.8% isoflurane for 3–4 h. EEG recordings, R-MUA and behaviour were observed for 1–3 h, during both wakefulness and sleep, every day for 5–7 days after anaesthesia. None of the cats showed abnormal behaviour, or EEG or R-MUA abnormalities after any of the anaesthetics, not only during wakefulness but during slow-wave and paradoxical phases of sleep. These results suggest that if seizures occur after anaesthesia, volatile anaesthesia itself may not be the cause. (*Br. J. Anaesth.* 1996; **76**: 721–725)

Key words

Anaesthetics volatile, sevoflurane. Anaesthetics volatile, enflurane. Anaesthetics volatile, isoflurane. Brain, electroencephalography. Complications, convulsions.

Sevoflurane is a new volatile anaesthetic in current popular use in Japan. Using cats with chronically implanted brain electrodes, we have reported that sevoflurane suppresses central nervous system (CNS) background electrical activities and leaves reactive capability relatively unaffected during light planes of anaesthesia but facilitates it in deep anaesthesia to produce an epileptoid state [1]. These neurophysiological properties of sevoflurane are similar to those of enflurane which also induces convulsions in deep anaesthesia [1].

Using cats with chronically implanted brain electrodes, Julien and Kavan reported epileptiform electroencephalogram (EEG) activities and abnormal behaviour after enflurane anaesthesia: the epileptic actions appeared on the second, peaked on the fourth and disappeared by the 16th day after anaesthesia [2]. However, such postanaesthetic neurological sequelae of enflurane were not reproduced in cats and humans by other investigators [3–5]. Nevertheless, the postanaesthetic epileptic effects are controversial in humans because many clinical cases of postanaesthetic seizure have been reported [6–16].

As sevoflurane has an epileptogenic property in deep anaesthesia [1], it is more than scientific interest to examine if sevoflurane has neurological or epileptoid effects in the postanaesthetic period. In this study, we recorded serial EEG before, during and after sevoflurane, enflurane and isoflurane anaesthesia in cats with chronically implanted brain electrodes, and examined the EEG and behavioural effects for 5–7 days after anaesthesia. It is well known that an abnormal EEG becomes manifest during light sleep in epileptic patients and amygdaloid kindled cats [17–22]. Therefore, EEG patterns were compared not only during wakefulness, but during slow-wave and paradoxical phases of sleep.

Materials and methods

Five cats of both sexes, weighing 2.3–4.1 kg, were used in this study, which was approved by our Institutional Animal Research Committee. The anaesthetic agents studied were sevoflurane ($n = 5$), enflurane ($n = 5$) and isoflurane ($n = 3$). At least 2 weeks after implantation of brain electrodes, each anaesthetic was administered to the cats with intervals greater than 4 weeks. EEG activities of wakefulness and sleep were studied before and after anaesthesia. The overall timetable of the experiment on each cat is shown in figure 1.

PLACEMENT OF ELECTRODES

The surgical procedures were performed during pentobarbitone anaesthesia (40 mg kg^{-1} i.p.). Cats were placed on a stereotaxic apparatus and electrodes implanted over the frontal sinus, parietal cortex, occipital cortex and in the amygdala (A:12, L:11, D:−6), dorsal hippocampus (A:2, L:9, D:9) and midbrain reticular formation (A:2, L:±3, D:−2),

---

JIRO KURATA, MD, TAKEHIKO ADACHI, MD, SHIN-ICHI NAKAO, MD, MASAHIRO MURAKAWA, MD, TSUTOMU SHICHINO, MD, MASATOSHI SHIBATA, MD, KENJIRO MORI, MD, FRCA, Department of Anaesthesia, Kyoto University Hospital, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-01, Japan. Accepted for publication: December 11, 1995.

Correspondence to K.M.

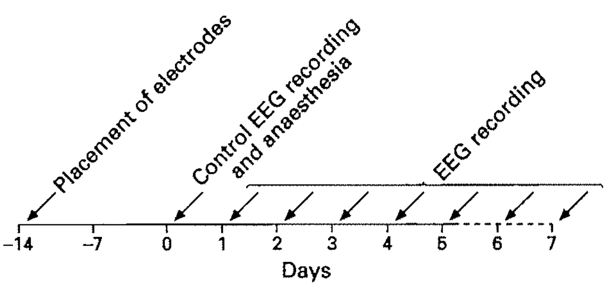


Figure 1 Schematic representation of the experimental schedule for each cat. Day 0 = day of anaesthetic administration and control electroencephalogram (EEG) recording.

according to the atlas of Snider and Niemer [23]. The cortical electrodes were made of stainless steel screws, 2 mm in diameter, and the subcortical bipolar electrodes were made of side-by-side stainless steel wires, 0.2 mm in diameter, insulated with epoxy resin except for the cut-end tips. The distance between the tips was 0.5–1.0 mm. Electrode position in the limbic structures was confirmed by probing the EEG activities: the electrodes were advanced by 1-mm steps until seizure activity appeared on the EEG [1]. This seizure was induced by an injury discharge, typical of the limbic structures [1]. All leads were soldered to a miniature vacuum tube socket, which was fixed to the skull with dental cement. During recording of CNS electrical activities, the socket was connected to the recording devices with a bundle of flexible cables of 5 m in length to allow for free movement of the cats.

ADMINISTRATION OF ANAESTHETICS

Initially the cats were anaesthetized with either 5 % sevoflurane, 5 % enflurane or 5 % isoflurane in oxygen, in a small anaesthesia box. The trachea was intubated without the use of neuromuscular blocking agents. The lungs were ventilated artificially with an animal respirator (SN-480-5, Shinano, Tokyo). The inspired concentration of sevoflurane, enflurane or isoflurane was adjusted to 5.0 %, 3.5 % or 4.8 %, respectively, using the Anaesthetic Gas Monitor (Type 1304, Brüel and Kjær, Nærum, Denmark), and end-tidal carbon dioxide tension was maintained at 4.0–4.7 kPa [24]. These selected concentrations of sevoflurane and enflurane are known to induce EEG seizures [1, 25], and that of isoflurane to induce isoelectric EEG with sporadic spikes [26]. Body temperature was maintained at 37–38 °C with a heated water mattress [24]. Duration of anaesthesia was 3–4 h. After recovery from anaesthesia, the tracheal tube was removed and the cats kept in a EEG recording box (90 × 60 × 70 cm).

RECORDING OF CNS ELECTRICAL ACTIVITIES

Preanaesthetic control and postanaesthetic recordings of EEG and reticular multiunit activity (R-MUA) were made during three behavioural states of wakefulness, and slow-wave and paradoxical phases of sleep. These recordings lasted 1–3 h. The EEG and R-MUA were recorded for 1–3 h, every day, for 5–7 days after anaesthesia. We considered that observation for the first 5 days after anaesthesia would be sufficient to identify any possible neurological abnormality [2]. During the recording, behavioural changes were confirmed by visual observation through a one-way window of the EEG recording box, and EEG changes were correlated with either wakefulness, slow-wave or paradoxical phases of sleep. These CNS electrical activity recordings were performed between 10:00 and 17:00.

Cortical and subcortical EEG were recorded on an eight-channel polygraph (Recti-Horiz-8K, San-ei, Tokyo) at a recording paper speed of 10 mm s^{-1}. The frontal sinus electrode was used as a reference for the cortical EEG. The subcortical EEG were recorded with the bipolar depth electrodes. The time constant was set at 0.1 s and the high-cut filter at 100 Hz.

The R-MUA was measured according to the method described previously [27]. The depth bipolar electrode implanted in the midbrain reticular formation differentially recorded discharge of a population of neurones included in an area with a radius of approximately 1 mm around the tip of the electrode. The wide-band signal obtained was amplified (1205C, San-ei, Tokyo) and then sent to a high-frequency band-pass filter, the peak frequency response of which was centred at 1300 Hz, with 3-dB attenuation at 600 and 2500 Hz. This high-frequency activity was rectified and smoothed with an electronic circuit (envelope detector), with a smoothing time constant of 50 ms, and was expressed as an oscillation of direct current (DC) voltage: the higher the DC level, the greater the firing of a population of neurones. This signal was recorded on a paper recorder (Rectigraph-8K, San-ei, Tokyo) at a speed of 5 mm min^{-1}. The noise level of the recording system was estimated as the distance between the DC level obtained by inserting a 10-kΩ resistor and that obtained by inserting a short across the input in place of the animal. The R-MUA level was measured as the distance from the lower limit of the multi-unit tracing to the 10-kΩ resistor line. The signal-to-noise ratio exceeded 10 in all cases.

Results

Before anaesthesia, all cats showed alternating patterns of typical EEG activities of wakefulness, and slow-wave and paradoxical phases of sleep. Inhalation of the anaesthetics induced EEG activities characteristic of each agent [1, 26]. During enflurane anaesthesia we were able to induce EEG seizures by auditory stimulation by clapping hands [25], but not during sevoflurane or isoflurane anaesthesia.

EEG activities before and after anaesthesia with each anaesthetic did not differ. Characteristic patterns of EEG alternated, coinciding with each of the three phases: wakefulness, slow-wave sleep and paradoxical sleep (fig. 2). These patterns were the same before and for the 5–7 days after anaesthesia. During wakefulness, there were theta waves and high-frequency small amplitude activities in the dorsal hippocampus, desynchronized activities in the cortex and relatively small amplitude activities in

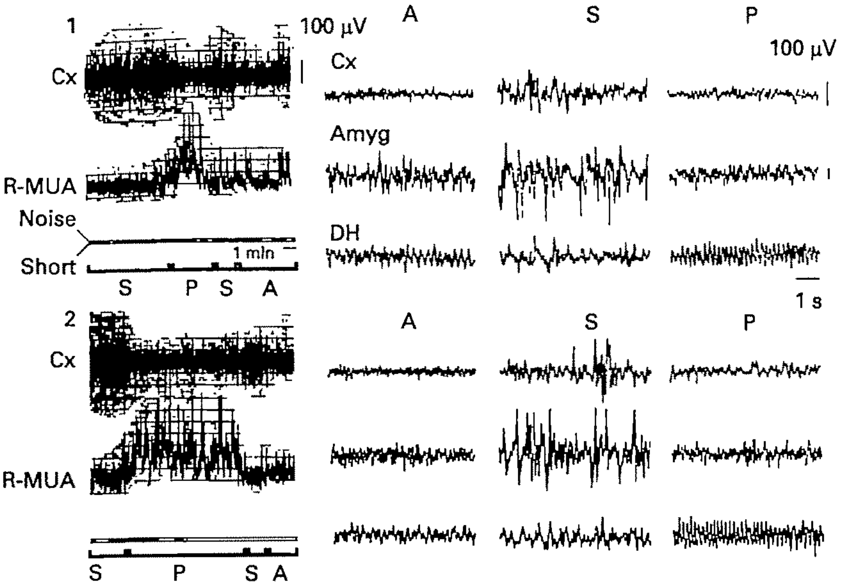


Figure 2 Representative patterns of EEG and reticular multi-unit activity (R-MUA) before (1) and 6 days after (2) sevoflurane anaesthesia. Note that there are three alternating types of states in R-MUA, that is awake (A), slow-wave sleep (S) and paradoxical sleep (P), of variable duration. The characteristic EEG in each state is shown on the right. Cx = Cerebral cortex, Amyg = amygdala, DH = dorsal hippocampus.

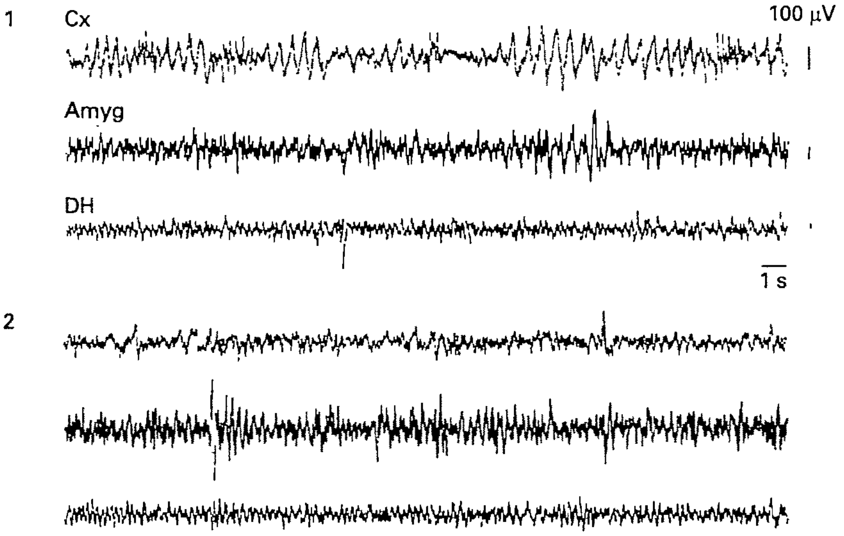


Figure 3 Characteristic EEG of a cat 6 days after sevoflurane anaesthesia when it was grooming (1) or eating (2). Cx = Cerebral cortex, Amyg = amygdala, DH = dorsal hippocampus.

the amygdala. During slow-wave sleep, large amplitude slow waves appeared in all leads and spindle bursts in the cortex. Most characteristics was large amplitude sharp waves in the amygdala but not in the other brain areas. During the paradoxical phase of sleep, small amplitude activities in the dorsal hippocampus disappeared leaving the 4–7 Hz theta waves more prominent, and the EEG of the cortex and amygdala were represented by desynchronized activities.

Large amplitude delta wave bursts sometimes appeared repetitively in the cortex during wakefulness, both before and after anaesthesia, when the cats were either grooming, drinking water or eating (fig. 3). These activities were, however, best understood as movement artefacts. Large amplitude spikes appeared in any lead of the cortex, amygdala and dorsal hippocampus when the cats moved the head in grooming, drinking or eating. These large amplitude spike-like activities did not synchronize with those of the other brain areas.

The R-MUA changed in a characteristic manner according to the three phases stated above: the averaged R-MUA was largest during the paradoxical phase of sleep, smaller during wakefulness, and smallest during slow-wave sleep. Figure 2 shows typical tracings of R-MUA before and after anaesthesia, which did not differ. The intermittent bursts of cortical EEG during wakefulness were usually associated with gross body movements.

The behaviour of the cats was normal and no movements implicating abnormal CNS activities were noted throughout the postanaesthetic period. They remained tame and in good temper as before anaesthesia.

Discussion

This study has confirmed the absence of an abnormal EEG and abnormal behaviour after sevoflurane, enflurane and isoflurane anaesthesia, not only during wakefulness but during slow-wave and paradoxical sleep throughout the postanaesthetic period. The anaesthetic concentrations of sevoflurane and enflurane were in the convulsive range [1, 25]. These findings indicate that these anaesthetics did not induce an epileptoid state after anaesthesia. This is the first study that provides evidence that sevoflurane does not cause persistent postanaesthestic EEG or behavioural abnormalities.

Julien and Kavan first reported the central nervous system effects of enflurane in cats with chronically implanted brain electrodes [2]. They observed residual behavioural and electroencephalographic abnormalities on the second day after anaesthesia and these abnormalities persisted for 14–16 days. Their cats appeared to be frightened, resisted handling and, at the same time, large amplitude spike activities were observed in the cerebral cortex and thalamic nuclei. Such abnormal EEG peaked at day 4, the intensity and frequency of the spike activity decreased by day 8, and the EEG returned to normal by day 16 [2]. Their study was contradicted by a series of other studies. Bassell and co-workers [5] conducted 2 MAC h of enflurane anaesthesia in cats with chronically implanted brain electrodes and observed no abnormal EEG or behaviour for 4 weeks after anaesthesia. Heavner and Amory [4] reported that seizure-inducing thresholds for lignocaine and pentylenetetrazol were not reduced after anaesthesia with 4% enflurane for 2 h over the 4 successive days in cats with chronically implanted brain electrodes. They also reported the absence of behavioural or EEG changes suggestive of long-lasting effects of enflurane exposure [4]. In humans, Burchiel and co-workers were not able to observe *de novo* epileptoid EEG after 9.6 MAC h of enflurane anaesthesia in 12 volunteers for 30 days [3]. However, these earlier studies [3–5], and those of Julien and Kavan on enflurane [2] and isoflurane [28], did not observe EEG during sleep. It is well known that drowsiness and sleep increase the probability of finding epileptiform discharges in the EEG of epileptic patients [17–21], and the EEG of natural or soporific-induced sleep is examined routinely, especially in temporal lobe seizures and nocturnal seizures [20]. In this study we demonstrated the absence of abnormal EEG not only during wakefulness but also during slow-wave and paradoxical phases of sleep after sevoflurane, enflurane and isoflurane anaesthesia.

In the present study, the EEG appeared normal throughout the postanaesthetic period, and large amplitude spike activity was always associated with either slow-wave sleep in the limbic structures or body movements such as grooming, drinking or eating. The large amplitude delta wave bursts, similar to the so-called hypersynchronous delta rhythm, pathognomonic for epilepsy [20], were observed when the cats were grooming, drinking or eating. Such activity is usually provoked by hyperventilation in epileptic patients [20]. This activity resembled the abnormal EEG activities reported by Julien and Kavan [2]. In their experiments no myoclonic movement linked with the abnormal EEG was noted, and movement artefacts might possibly have been misinterpreted as abnormal EEG. In the present study this type of activity appeared even before anaesthesia during head movement, and may be explained by head movement, that is movement artefacts. The cats remained tame, in good temper, with a good appetite and showed no resistance to handling or a frightened appearance such as Julien and Kavan had described [2].

Our experimental conditions were a little different from those of Julien and Kavan [2]. They conducted enflurane anaesthesia during spontaneous ventilation via a face mask with a 2:1 mixture of air and oxygen, while we conducted anaesthesia via a tracheal tube and artificial ventilation with oxygen. They administered 4.5–5.5% enflurane for approximately 30 min, while we gave 3.5% enflurane for 3–4 h. We chose this concentration of enflurane because induction of seizures is known to be easiest with 3.5% enflurane [25]. If the cause of the persistent abnormality of EEG and behaviour in their experiment was the metabolite(s) of enflurane as they suggested, such a metabolite(s) would accumulate more during a longer period of anaesthesia and would tend to induce abnormalities. Therefore, our experimental condition should have been more likely to induce persistent abnormalities in the EEG or behaviour.

Enflurane, during deep anaesthesia, is known to induce an epileptoid state in humans [29, 30] and cats [26], characterized by suppression of background reticular cell firing and augmentation of the reactive capability of the brain [26]. Although there have been several clinical reports of seizures after enflurane anaesthesia [6–15], in this study we may speculate that enflurane itself might not have been the causative agent.

Sevoflurane was confirmed to have similar neurophysiological properties to enflurane in cats [1]. It induces seizures during deep anaesthesia by somatic stimulation, although less frequently than enflurane [1]. In humans, however, a sevoflurane-induced epileptoid state has not yet been reported, and there has been no report of seizure after sevoflurane anaesthesia.

The convulsive property of isoflurane is less potent than that of enflurane in cats [26]. It does not induce seizures even during deep anaesthesia marked by isoelectric EEG with spikes in cats [26] or by isoelectric EEG in humans [31]. Clinically there is only one case report of seizure just after isoflurane anaesthesia, which was characterized by myoclonus [16].

In conclusion, we did not observe abnormal behaviour or epileptic EEG after sevoflurane, enflurane and isoflurane anaesthesia, not only during wakefulness, but also during slow-wave and paradoxical phases of sleep. These results suggest that even convulsant anaesthetics do not produce an epileptoid state after anaesthesia, and if seizures occur after anaesthesia, the anaesthetic itself may not be the cause of the seizure.

References

1. Osawa M, Shingu K, Murakawa M, Adachi T, Kurata J, Seo N, Murayama T, Nakao S, Mori K. Effects of sevoflurane on central nervous system electrical activity in cats. *Anesthesia and Analgesia* 1994; **79**: 52–57.
2. Julien RM, Kavan EM. Electrographic studies of a new volatile anesthetic agent: enflurane (Ethrane). *Journal of Pharmacology and Experimental Therapeutics* 1972; **183**: 393–403.
3. Burchiel KJ, Stockard JJ, Calverley RK, Smith NT. Relationship of pre- and postanesthetic EEG abnormalities to enflurane-induced seizure activity. *Anesthesia and Analgesia* 1977; **56**: 509–514.
4. Heavner JE, Amory DW. Lidocaine and pentylenetetrazol seizure thresholds in cats are not reduced after enflurane anesthesia. *Anesthesiology* 1981; **54**: 403–408.
5. Bassell GM, Cullen BF, Fairchild MD, Kusske JA. Electroencephalographic and behavioural effects of enflurane and halothane anaesthesia in the cat. *British Journal of Anaesthesia* 1982; **54**: 659–663.
6. Ohm WW, Cullen BF, Amory DW, Kennedy RD. Delayed seizure activity following enflurane anesthesia. *Anesthesiology* 1975; **42**: 367–368.
7. Kruczek M, Albin MS, Wolf S, Bertoni JM. Postoperative seizure activity following enflurane anesthesia. *Anesthesiology* 1980; **53**: 175–176.
8. Ng ATH. Prolonged myoclonic contractions after enflurane anaesthesia—a case report. *Canadian Anaesthetists Society Journal* 1980; **27**: 502–503.
9. Jenkins J, Milne AC. Convulsive reaction following enflurane anaesthesia. *Anaesthesia* 1984; **39**: 44–45.
10. Allan MWB. Convulsions after enflurane. *Anaesthesia* 1984; **39**: 605–606.
11. Yazji NS, Seed RF. Convulsive reaction following enflurane anaesthesia. *Anaesthesia* 1984; **39**: 1249.
12. Nicoll JVM. Status epilepticus following enflurane anaesthesia. *Anaesthesia* 1986; **41**: 927–930.
13. Grant IS. Delayed convulsions following enflurane anaesthesia. *Anaesthesia* 1986; **41**: 1024–1025.
14. Fahy LT. Delayed convulsions after day case anaesthesia with enflurane. *Anaesthesia* 1987; **42**: 1327–1328.
15. Parke TJ, Jago RH. Focal seizure following enflurane. *Anaesthesia* 1992; **47**: 79–80.
16. Harrison JL. Postoperative seizures after isoflurane anesthesia. *Anesthesia and Analgesia* 1986; **65**: 1235–1236.
17. Kellaway P. Sleep and epilepsy. *Epilepsia* 1985; **26** (Suppl. 1): S15–S30.
18. Feijoo M, Bilbao J. Seizures of sleep onset: clinical and therapeutical aspects. *Clinical Neuropharmacology* 1992; **15**: 50–55.
19. Montplaisir J, Laverdière M, Saint-Hilaire JM, Walsh J, Bouvier G. Sleep and temporal lobe epilepsy: a case study with depth electrodes. *Neurology* 1981; **31**: 1352–1356
20. Binnie CD, Prior PF. Electroencephalography. *Journal of Neurology, Neurosurgery and Psychiatry* 1994; **57**: 1308–1319.
21. Steriade M, Contreras D, Amzica F. Synchronized sleep oscillations and their paroxysmal developments. *Trends in Neurosciences* 1994; **17**: 199–208.
22. Hiyoshi T, Seino M, Kakegawa N, Higashi T, Yagi K, Wada JA. Evidence of secondary epileptogenesis in amygdaloid overkindled cats: electroclinical documentation of spontaneous seizures. *Epilepsia* 1993; **34**: 408–415.
23. Snider RS, Niemer WT. *A Stereotaxic Atlas of the Cat Brain*. Chicago: University of Chicago Press, 1961.
24. Herbert DA, Mitchell RA. Blood gas tensions and acid-base balance in awake cats. *Journal of Applied Physiology* 1971; **30**: 434–436.
25. Stevens JE, Fujinaga M, Oshima E, Mori K. The biphasic pattern of the convulsive property of enflurane in cats. *British Journal of Anaesthesia* 1984; **56**: 395–403.
26. Ogawa T, Shingu K, Shibata M, Osawa M, Mori K. The divergent actions of volatile anaesthetics on background neuronal activity and reactive capability in the central nervous system in cats. *Canadian Journal of Anaesthesia* 1992; **39**: 862–872.
27. Mori K, Winters WD. Neural background of sleep and anesthesia. *International Anesthesiology Clinics* 1975; **13**: 67–108.
28. Julien RM, Kavan EM. Electrographic studies of isoflurane (Forane). *Neuropharmacology* 1974; **13**: 677–681.
29. Neigh JL, Garman JK, Harp JR. The electroencephalographic pattern during anesthesia with Ethrane: effects of depth of anesthesia, $PaCO_2$, and nitrous oxide. *Anesthesiology* 1971; **35**: 482–487.
30. Lebowitz MH, Blitt CD, Dillon JB. Enflurane-induced central nervous system excitation and its relation to carbon dioxide tension. *Anesthesia and Analgesia* 1972; **51**: 355–363.
31. Eger E II, Stevens WC, Cromwell TH. The electroencephalogram in man anesthetized with Forane. *Anesthesiology* 1971; **35**: 504–508.

British Journal of Anaesthesia 1996; **76**: 726–730

REVIEW ARTICLE

Prehospital monitoring of trauma patients: experience of a helicopter emergency medical service

A. P. MORLEY

The Helicopter Emergency Medical Service (HEMS) began operating from the Royal London Hospital in 1989. It remains the only medically staffed helicopter for the retrieval of major trauma victims in the UK. Its aim is to optimize early management and ensure rapid transport to appropriate specialist centres. When necessary, patients are anaesthetized, the trachea intubated and the lungs ventilated manually on scene. Trauma, and ensuing therapy, may be accompanied by significant physiological change. The aims of monitoring are to improve patient safety, increase the likelihood of early, accurate diagnosis, and allow assessment of subsequent treatment.

Monitors for prehospital use

The recommendations of the Association of Anaesthetists for minimal standards of monitoring in anaesthesia are well known. Continuous monitoring of cardiovascular and respiratory function is essential [2]. In addition, a recent working party has produced a report on patient management during helicopter transport, including recommendations for monitoring [6]. Both refer to the uninterrupted presence of an appropriately trained doctor throughout. Table 1 illustrates monitors that HEMS apply on arrival at scene and subsequently in the helicopter, where mechanical ventilation is often commenced. Weight limitations on equipment carried by HEMS in the aircraft and thence to scene has led to the exclusion of some otherwise desirable monitors.

Equipment for use on board aircraft requires Civil Aviation Authority (CAA) approval specific to the type and model of the aircraft in which it is to be used. Each item of monitoring equipment must be tested by a CAA approved organization [11] to exclude any potential hazards, for example fire, smoke, explosion or interference with aircraft communication and navigation systems. While the helicopter is thus unaffected by the monitor, the reverse is not necessarily the case. General monitoring problems encountered in flight, and before this in the field, are summarized in table 2.

Some qualities are desirable in monitors for use in the prehospital environment and in patient transfer (table 3). Portable multimodal monitors are available from several manufacturers, including Siemens, Datascope, Datex and PaceTech. HEMS uses the Propaq 106EL (Protocol Systems, Inc., Beaverton, OR, USA). It measures 16.3 cm by 20.5 cm by 16.8 cm and weighs 3.8 kg. Its minimum battery life is 4 h and it has electrocardiogram (ECG), non-invasive arterial pressure (NIAP), oxygen saturation (Sp_{O_2}), end-tidal carbon dioxide (PE'_{CO_2}) and temperature measurement facilities.

ELECTROCARDIOGRAPHY

ECG monitoring is a fundamental part of most resuscitation procedures. It assists the on scene diagnosis of electromechanical dissociation (EMD), arrhythmias, and myocardial injury and ischaemia. EMD may occur in trauma patients with tension pneumothoraces and hypovolaemia. Myocardial injury from blunt chest trauma may cause arrhythmias or more subtle ST segment deviations, the interpretation of which requires caution. Normal individuals can exhibit ST segment deviation on standard prehospital cardiac monitoring equipment during routine transport [22]. ECG monitoring is prone to mechanical and electrical interference, both on scene and in transit. In addition, adhesive electrodes often become detached in the rain or if blood runs onto the chest.

NON-INVASIVE ARTERIAL PRESSURE

On scene, frequent, automated NIAP monitoring helps in the early detection of hypotension, although this is a late sign of shock in the young. NIAP monitoring enables detection of hypertension accompanying increased intracranial pressure in head injured patients. The efficacy of attempts to obtund the hypertensive response to on scene laryngoscopy and intubation may also be assessed. There are several practical problems with NIAP cuff application in the field. These include lack of access where patients are trapped. Clothing usually needs to be cut and underlying limbs may be injured. When the cuff has been applied, patient movement or vibration from extrication tools may prevent accurate readings.

In helicopter transit, oscillometric readings in critically ill patients are not as reliable as direct invasive monitoring and are, in some instances,

(*Br. J. Anaesth.* 1996; **76**: 726–730)

Key words

Anaesthesia, audit. Anaesthesia, emergency service. Complications, trauma. Equipment, monitors.

A. P. MORLEY, BA, MB, BS, FRCA, Helicopter Emergency Medical Service, Royal London Hospital, Whitechapel, London E1 1BB. Present address for correspondence: Department of Anaesthesia and Intensive Care, Prince of Wales Hospital, Sha Tin, New Territories, Hong Kong.

Table 1 Recommended monitors for prehospital management and air transfer of trauma patients

On scene	In aircraft
Pulse oximeter	Continued use of on scene monitors
Electrocardiogram	
Automated NIAP	
In-line capnograph	Airway pressure monitor
Aural temperature probe	

Table 2 General monitoring problems in the prehospital management and air transfer of trauma victims

On scene	In aircraft
Environmental	
Rain	Noise
Cold	Vibration
Sunshine	Access
Noise	Electrical interference
Vibration	
Access to patient	
Distraction by events at scene	
Patient-related factors	
Injury preventing monitor application	
Displacement of sensors	
Unco-operative, confused patients	

Table 3 Desirable features in a prehospital monitor

- Accuracy
- Multimodality
- Long battery life with recharging facility
- Durability
- Ease of carriage
- Lightweight
- Reliability in adverse environmental conditions
- Ease of operation by attendant paramedical staff
- Compatibility with equipment at receiving hospitals
- Printer/downloading facility
- Ease of service or part replacement
- Low cost

unobtainable [35]. This may also be because of vibration. In a study by Campbell and colleagues [7] comparing methods of neonatal transport, helicopters in flight were found to produce overall vibration levels of 5.6 m sq s^{-1} in the vertical axis, with least vibration occurring in cruising fixed-wing aircraft (0.04 m sq s^{-1}). During HEMS helicopter transfers, NIAP monitoring is prone to intermittent malfunction. While invasive arterial pressure monitoring may be more accurate and reliable, the aim is to treat and transport casualties as quickly as possible from the scene to the appropriate hospital. Extra time taken attempting roadside arterial cannulation may not be in the patient's best interests.

TEMPERATURE

HEMS uses an aural probe, compatible with the Propaq 106EL, to measure core temperature. This is reasonably well tolerated by conscious patients. It indicates the presence of initial hypothermia and monitors the response to corrective manoeuvres. In trauma patients, core and mean body temperatures are inversely related to severity of injury [34]. For a given level of injury, mortality is increased in trauma patients who develop hypothermia. This is the case whether hypothermia is defined as a core temperature below 34 °C, 33 °C or 32 °C [27]. Patients often sustain injuries outdoors and may suffer prolonged exposure to cold as a result of entrapment in vehicles. Clothing may be cut or removed in order to assess the nature and extent of the injury. Attempts to reduce heat loss at scene include the use of warmed i.v. fluids and reflective insulation blankets. In the helicopter, the cabin is heated by bleeding hot air from the engine compression system. This affects engine performance slightly so heating is not possible during take off or landing.

OXYGEN SATURATION

Pulse oximetry has numerous applications in hospital monitoring and an established place in anaesthesia. Several articles have indicated its usefulness in the prehospital environment, both on scene [36, 50] and in helicopter transfers [49, 54]. Its principal application for the field anaesthetist is detection of hypoxia, which may prompt a decision to induce anaesthesia and intubate the trachea. More controversially, some authors have suggested it has a role in monitoring circulation and assessment of systolic arterial pressure.

Independently, but especially in conjunction with hypotension, hypoxia is recognized as a major extracranial variable influencing outcome in severely head injured patients [10]. Early tracheal intubation of these patients should reduce the likelihood of hypoxia and hypercapnia and may prevent secondary brain injury. In one emergency department study, a group of patients monitored with continuous pulse oximetry while undergoing emergency intubation had a lower likelihood of hypoxic episodes and a shorter duration of severe hypoxia than an unmonitored group [38]. Pulse oximetry has also proved useful in the early detection and management of tension pneumothorax [30], and in other conditions encountered regularly by HEMS, such as severe lung contusions and haemothorax.

Some authors believe that the pulse oximeter is valuable for distal circulatory monitoring in injured limbs. The use of oximetry in the hospital treatment of supracondylar humeral fractures has been reported [5, 40]. However, a prospective study of oximetric monitoring of distal circulation in fractured limbs before and after manipulation showed it had no clear role [15]. In the diagnosis of failing perfusion caused by increased intracompartmental pressure, oximetry is unreliable [37]. This is not surprising. Pulse oximeter signals can be obtained from fingers where Doppler studies indicate only 4% flow [32], suggesting that a plethysmographic trace is no guarantee of effective blood flow to the tissues. This may explain why, while the benefits of oximetry in the management of primary respiratory arrest seem clear, its value in monitoring resuscitation from cardiac arrest is doubtful [51], despite anecdotal reports [39].

As discussed above, there are some circumstances where oscillometric arterial pressure measurement is difficult. The reappearance of a plethysmographic waveform from a distal pulse oximeter probe on deflation of an arterial pressure cuff has been used to measure systolic arterial pressure in hospitalized neonates [31] and it compared favourably with oscillometric measurements. A similar method has also been used with some success in adults [9] and in patients transferred by helicopter [53]. Unfortunately, the accuracy and reliability of the technique used in the last study were not compared with those of the oscillometric method.

Environmental factors affecting pulse oximeter function

Several environmental factors limit the usefulness of pulse oximetry in the prehospital management of trauma patients. While ambient artificial light can cause inaccurate readings [16], the effect of direct sunlight is unknown, although it certainly reduces the visibility of LED display panels. Probe displacement is common. Where this is incomplete, spuriously low Sp_{O_2} readings may occur in normoxic subjects even when heart rate is displayed correctly [29]. In hypoxic subjects, various inaccuracies may result. Importantly, some oximeters display falsely high Sp_{O_2} values at low saturations [3]. Noise on scene may drown the pulse signal. Even in experimental conditions, the change in pitch accompanying desaturation in most oximeters is detected better by some subjects than others [45].

Oximeter readings fail frequently during helicopter transit. A recent study of pulse oximetry in a German air rescue service found that more than 25% of measurement time was subject to interference [23]. Some oximeters incorporate weighted averaging systems to filter out suspect values while enabling a rapid response to changing Sp_{O_2} [56]. By using ECG synchronization, which is a feature of the Propaq 106EL, Helm and colleagues [24] achieved more than an eight-fold reduction in passive motion artefacts in oximetric monitoring during emergency helicopter patient transfer.

Patient factors affecting pulse oximeter function

Trauma victims out of hospital are not prepared in the same way as patients before operation. Although pulse oximeter readings are unchanged by dried blood [42] and most shades of nail polish [14], oximeter failure has occurred in some HEMS patients with fingers covered in oil or bitumen.

Clinical circumstances influence interpretation of oximeter readings. Burns accounted for about 5% of the HEMS workload in 1994 and, at present, there are no facilities for measuring carboxyhaemoglobin (HbCO) on the aircraft. In the presence of HbCO, the fractional oxygen saturation is overestimated by pulse oximetry [41]. Despite absorption spectra differences between oxyhaemoglobin and HbCO, the degree of overestimation is close to the percentage of HbCO in most cases. This has been shown *in vitro* [41], in animal studies [4] and clinically for HbCO values of 1–30% [55].

Blood loss is common in trauma victims. In the presence of normoxia, acute severe anaemia, with haemoglobin concentrations as low as 2.3 g dl^{-1}, does not significantly affect the accuracy of pulse oximetry [26]. However, at an oxygen saturation of less than 80%, anaemia approximately doubles the error of pulse oximeters [46]. HEMS does not carry blood, and patients are resuscitated, where appropriate, with warmed crystalloid or colloid solutions. The resulting haemodilution may exacerbate any decrease in haemoglobin concentration.

Where blood loss and hypothermia coexist, the resulting peripheral vasoconstriction increases the hypotensive failure threshold of pulse oximeters [48]. Under conditions of poor perfusion, a comparison of 20 pulse oximeters showed variable performance, with all but two models failing on occasion. Where readings were obtained, mean differences from corresponding co-oximeter readings were less than 5% [12]. The same group compared the performance of finger, nose, ear and forehead probes, under similar conditions, all of which are carried by HEMS. Their conclusion was that the overall performance of probes in sites other than the finger was worse [13]. Interestingly, there is some evidence that under conditions of profound hypoxia, another clinical state encountered frequently by HEMS, ear probes respond more rapidly and more accurately than finger probes [47].

The accuracy of pulse oximetry may be affected adversely by both patient and environmental factors. The clinical relevance of this may not be immediately apparent, given that 100% oxygen is administered to most trauma victims as soon as ambulance crews or HEMS arrive. However, the first oximetric readings may influence the decision to intubate the trachea or insert chest drains. At present, initial ventilatory frequency, systolic arterial pressure and Glasgow coma scale are used to compile the revised trauma score. This enables the physiological state of trauma victims to be compared and has some predictive value [8]. In future, it is possible that initial oxygen saturation may also be used in this way and accurate measurement will assume even greater importance.

END-TIDAL CARBON DIOXIDE

Portable methods of PE'_{CO_2} measurement are limited to disposable colorimetric devices or in-line analysers, which may be incorporated into multimodal monitors such as the Propaq.

An example of the former is the Easy Cap (Nellcor Incorporated, Hayward, CA, USA). This incorporates metocresol purple as an indicator that changes colour from purple to yellow in the presence of carbon dioxide. A colour scale allows distinction between the following ranges of PE'_{CO_2}; "A" purple, 0.03 to <0.05%; "B" tan, 0.5–2%; "C" yellow, 2–5%. In patients whose tracheas are intubated correctly, the indicator colour cycles from purple (inspiration) to yellow (expiration). The detector has an internal volume of 38 ml, a flow resistance of 3 ± 1 cm H_2O at 60 litre min^{-1} and weighs less than 30 g. It ceases to function if the indicator strip becomes moist. This is a significant limitation in traumatized patients, where the airway may be soiled with blood, sputum, gastric contents, pulmonary oedema or tracheally administered drugs.

On scene capnometry assists confirmation of tracheal intubation, assessment of cardiopulmonary resuscitation, monitoring of deliberate hyperventilation and diagnosis of circuit disconnection.

Reliable confirmation of tracheal intubation is essential in unfavourable prehospital intubating conditions. Before medical staff arrive, the trachea is sometimes intubated by paramedics who may not recognize oesophageal placement [52]. Chest auscultation is often unsatisfactory because of noise, for example extrication equipment, and $P\mathrm{E}'_{CO_2}$ measurement, as in the operating theatre, is the best method. In one hospital study, a disposable device allowed more rapid confirmation of tracheal intubation than capnography. Speed of detection of oesophageal intubation was not significantly different for the two methods, and there were no false positive or false negative results with the colorimetric method [21]. Cautious interpretation is advisable in the field, whichever method is used. Recent ingestion of beer leads to high oesophageal $P\text{CO}_2$ in dogs [19]. In addition, manual bag and mask ventilation by paramedics is common. This produces initial, high "expired" $P\text{CO}_2$ readings where the oesophagus is subsequently intubated [33].

During cardiopulmonary resuscitation, the increase in $P\mathrm{E}'_{CO_2}$ that accompanies the return of spontaneous circulation is detectable with a disposable capnometer [25] and is often the first clinical indicator of the event [20]. The capnograph may herald the onset of circulatory arrest [17] and even indicate the efficacy of external cardiac massage [28]. $P\mathrm{E}'_{CO_2}$ depends on alveolar ventilation and pulmonary circulation. Where the former varies, as might be expected in roadside patients whose lungs are ventilated manually, assessment of pulmonary circulation by $P\mathrm{E}'_{CO_2}$ measurement should not logically be reliable. However, in one hospital study where arrested patients underwent manual ventilation, minimum $P\mathrm{E}'_{CO_2}$ values during CPR were predictive of resuscitation outcome and survival [44].

Capnography may be used to monitor the deliberate hyperventilation of head injured patients, when the trachea has been intubated on scene. Although the accuracy of most capnometers deteriorates even with a relatively modest increase in ventilatory frequency, in-line analysers of the type supplied for the Propaq 106EL are less prone to this than the sampling types [18]. During deliberate hyperventilation, interpretation of $P\mathrm{E}'_{CO_2}$ readings usually relies on the assumption that they accurately reflect arterial partial pressures of carbon dioxide (Pa_{CO_2}). This assumption may be rendered invalid by the physiological state of trauma victims. Askrog and colleagues, for example, demonstrated the increase in $Pa_{CO_2}-P\mathrm{E}'_{CO_2}$ gradient in anaesthetized patients deliberately rendered hypotensive [1]. More significant, perhaps, is a recent study of normovolaemic patients with multiple trauma undergoing mechanical ventilation [43] where the authors established a consistent Pa_{CO_2} to $P\mathrm{E}'_{CO_2}$ correlation across the study population. However, there was no correlation in 22% of individual patients, the frequency of a linear correlation was only 41%, and the ability of $P\mathrm{E}'_{CO_2}$ changes to predict the direction of change of Pa_{CO_2} was in error in 27% of comparisons.

The risk of circuit disconnection in patients undergoing ventilation is greater in the relatively uncontrolled prehospital environment where patients are transferred repeatedly from one site, or mode of transport, to another. Chest wall movements may be obscured, and changes in ventilator tone rendered inaudible by environmental noise. The capnograph is a more reliable indicator of the integrity of a circuit.

Conclusion

Monitors are important in the prehospital management of trauma victims. They may provide information that determines treatment at scene or in transit. Where patients are anaesthetized at scene, the standard of physiological monitoring required does not differ from that in theatre and is approached by some of the recent, portable, multimodal monitors. None of these, however, incorporates an oxygen analyser. Oxygen cylinders frequently run out unnoticed because of the absence of a suitable alarm. Monitoring of equipment used in the field is still suboptimal in this respect.

The accuracy and reliability of monitors may be affected adversely by the prehospital environment and the nature of the patients and their injuries. For the attending physician to interpret monitor readings correctly, familiarity with the equipment, its principles of operation and its limitations is essential.

The principal aim of resuscitation in trauma victims is adequate delivery of oxygenated blood to the tissues. This is difficult to assess in the intensive care unit and even more so at the roadside. Currently available monitors can, at best, provide only a guide. It is hoped that future design modifications will overcome some of the problems with the monitors discussed in this review.

References

1. Askrog VF, Pender JW, Eckenhoff JE. Changes in physiological dead space during deliberate hypotension. *Anesthesiology* 1964; **25**: 744–751.
2. Association of Anaesthetists of Great Britain and Ireland. Recommendations for minimum standards of monitoring in anaesthesia and recovery (revised). London: Association of Anaesthetists of Great Britain and Ireland, 1994.
3. Barker SJ, Hyatt J, Shah NK, Kao YJ. The effect of sensor malpositioning on sensor accuracy during hypoxemia. *Anesthesiology* 1993; **79**: 248–254.
4. Barker SJ, Tremper KK. The effect of carbon monoxide inhalation on pulse oximetry and transcutaneous $P\text{O}_2$. *Anesthesiology* 1987; **66**: 677–679.
5. Best CJ, Woods KR. An aid to the treatment of supracondylar fracture of the humerus: brief report. *Journal of Bone and Joint Surgery* 1989; **71B**: 141.
6. Bristow, A, Baskett P, Dalton M, Ediss P, Evans I, Harris R, Leighton M, Martin L, Perry I, Roberts G, Scurr J, Skinner D, Strong J, Toff N, Wilson A. Medical helicopter systems—recommended minimal standards for patient management. *Journal of the Royal Society of Medicine* 1991; **84**: 242–244.
7. Campbell AN, Lightstone AD, Smith JM, Kirpalani H, Perlman M. Mechanical vibration and sound levels experienced in neonatal transport. *American Journal of Diseases of Childhood* 1984; **138**: 967–970.
8. Champion HA, Sacco WJ, Copes WS, Gann DS, Gennarelli TA, Elanagan ME. A revision of the trauma score. *Journal of Trauma* 1989; **29**: 623–629.
9. Chawla R, Kumarvel V, Girdhar KK, Sethi AK, Indrayan A,

Bhattacharya A. Can pulse oximetry be used to measure systolic blood pressure? *Anesthesia and Analgesia* 1992; **74**: 196–200.

10. Chesnut RM, Marshall LF, Klauber MR, Blunt BA, Baldwin N, Eisenberg HM, Jane JA, Marmarou A, Foulkes MA. The role of secondary brain injury in determining outcome from severe head injury. *Journal of Trauma* 1993; **34**: 216–222.
11. Civil Aviation Publication 553 (Airworthiness procedures where the CAA has primary responsibility for type approval of the product). London: Civil Aviation Authority, 1991.
12. Clayton DG, Webb RK, Ralston AC, Duthie D, Runciman WB. A comparison of the performance of 20 pulse oximeters under conditions of poor perfusion. *Anaesthesia* 1991; **46**: 3–10.
13. Clayton DG, Webb RK, Ralston AC, Duthie D, Runciman WB. Pulse oximeter probes: a comparison between finger, nose, ear and forehead probes under conditions of poor perfusion. *Anaesthesia* 1991; **46**: 260–265.
14. Cote CJ, Goldstein EA, Fuchsman WH, Hoaglin DC. The effect of nail polish on pulse oximetry. *Anesthesia and Analgesia* 1988; **67**: 683–686.
15. David HG. Pulse oximetry in closed limb fractures. *Annals of the Royal College of Surgeons of England* 1991; **73**: 283–284.
16. Eisele JH, Downs D. Ambient light affects pulse oximeters. *Anesthesiology* 1987; **67**: 864–865.
17. Falk JL, Rackow EC, Weil MH. End-tidal carbon dioxide concentration during cardiopulmonary resuscitation. *New England Journal of Medicine* 1988; **318**: 607–611.
18. From RP, Scamman FL. Ventilatory frequency influences accuracy of end-tidal CO_2 measurements: analysis of seven capnometers. *Anesthesia and Analgesia* 1988; **67**: 884–886.
19. Garnett AR, Gervin CA, Gervin AS. Capnographic waveforms in esophageal intubation: effect of carbonated beverages. *Annals of Emergency Medicine* 1989; **18**: 387–390.
20. Garnett AR, Ornato JP, Gonzalez ER, Johnson EB. End-tidal carbon dioxide monitoring during cardiopulmonary resuscitation. *Journal of the American Medical Association* 1987; **257**: 512–515.
21. Goldberg JS, Rawle PR, Zehnder JL, Sladen RN. Colorimetric end-tidal carbon dioxide monitoring for tracheal intubation. *Anesthesia and Analgesia* 1990; **70**: 191–194.
22. Hebel GA, Hutton K, Kanowitz A, Neuman T, Martinson L, Rosen P. The accuracy of ST segment deviation in prehospital cardiac monitoring. *Journal of Emergency Medicine* 1994; **12**: 207–211.
23. Helm M, Forstner K, Lampl L, Bock KH. Pulse oximetry in the air rescue service. 1. Quantitative detection of interfering factors on the method. (German). *Anästhesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie* 1993; **28**: 86–90.
24. Helm M, Forstner K, Lampl L, Bock KH. Pulse oximetry in the air rescue service. 2. Methods of increasing the stability of pulse oximetry measurements—ECG synchronized pulse oximetry and adhesive sensors (German). *Anästhesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie* 1993; **28**: 174–178.
25. Higgins D, Hayes M, Denman W, Wilkinson DJ. Effectiveness of using end tidal carbon dioxide concentration to monitor cardiopulmonary resuscitation. *British Medical Journal* 1990; **300**: 581.
26. Jay GD, Hughes, L, Renzi FP. Pulse oximetry is accurate in acute anemia from hemorrhage. *Annals of Emergency Medicine* 1994; **24**: 32–35.
27. Jurkowich GJ, Greiser WB, Luterman A, Curreri PW. Hypothermia in trauma victims: an ominous predictor of survival. *Journal of Trauma* 1987; **27**: 1019–1024.
28. Kalenda Z. The capnogram as a guide to the efficacy of cardiac massage. *Resuscitation* 1976/1977; **6**: 259–263.
29. Kelleher JF, Ruff RH. The penumbra effect: vasomotion-dependent pulse oximeter artifact due to probe malposition. *Anesthesiology* 1989; **71**: 787–791.
30. Laishley RS, Aps C. Tension pneumothorax and pulse oximetry. *British Journal of Anaesthesia* 1991; **66**: 250–252.
31. Langbaum M, Eyal FG. A practical and reliable method of measuring blood pressure in the neonate by pulse oximetry. *Journal of Pediatrics* 1994; **125**: 591–595.
32. Lawson D, Norley I, Korbon G, Loeb R, Ellis J. Blood flow limits and pulse oximeter signal detection. *Anesthesiology* 1987; **67**: 599–603.
33. Linko K, Paloheimo M, Tammisto T. Capnography for detection of accidental oesophageal intubation. *Acta Anaesthesiologica Scandinavica* 1983; **27**: 199–202.
34. Little RA, Stoner HB. Body temperature after accidental injury. *British Journal of Surgery* 1981; **68**: 221–224.
35. Low RB, Martin D. Accuracy of blood pressure measurements made aboard helicopters. *Annals of Emergency Medicine* 1988; **17**: 604–612.
36. McGuire TJ, Pointer JE. Evaluation of a pulse oximeter in the prehospital setting. *Annals of Emergency Medicine* 1988; **17**: 1058–1062.
37. Mars M, Hadley GP. Failure of pulse oximetry in the assessment of raised limb intracompartmental pressure. *Injury* 1994; **25**: 379–381.
38. Mateer JR, Olson DW, Stueven HA, Aufderheide TP. Continuous pulse oximetry during emergency endotracheal intubation. *Annals of Emergency Medicine* 1993; **22**: 675–679.
39. Narang VPJ. Utility of the pulse oximeter during cardiopulmonary resuscitation. *Anesthesiology* 1986; **65**: 239–240.
40. Ray SA, Ivory JP, Beavis JP. Use of pulse oximetry during manipulation of supracondylar fractures of the humerus. *Injury* 1991; **21**: 103–104.
41. Reynolds KJ, Palayiwa E, Moyle JTB, Sykes K, Hahn CEW. The effect of dyshemoglobins on pulse oximetry: part I, theoretical approach and part II, experimental results using an in vitro test system. *Journal of Clinical Monitoring* 1993; **9**: 81–90.
42. Rosewarne FA, Reynolds KJ. Dried blood does not affect pulse oximetry. *Anaesthesia* 1991; **46**: 886–887.
43. Russell GB, Graybeal JM. Reliability of the arterial to end-tidal carbon dioxide gradient in mechanically ventilated patients with multi-system trauma. *Journal of Trauma* 1994; **36**: 317–322.
44. Sanders AB, Kern KB, Otto CW, Milander MM, Ewy GA. End-tidal carbon dioxide monitoring during cardiopulmonary resuscitation: a prognostic indicator for survival. *Journal of the American Medical Association* 1989; **262**: 1347–1351.
45. Schulte GT, Block FE jr. Can people hear the pitch change on a variable-pitch pulse oximeter? *Journal of Clinical Monitoring* 1992; **8**: 198–200.
46. Severinghaus JW, Koh SO. Effect of anemia on pulse oximeter accuracy at low saturation. *Journal of Clinical Monitoring* 1990; **6**: 85–88.
47. Severinghaus JW, Naifeh KH. Accuracy of response of six pulse oximeters to profound hypoxia. *Anesthesiology* 1987; **67**: 551–558.
48. Severinghaus JW, Spellman MJ. Pulse oximeter failure thresholds in hypotension and vasoconstriction. *Anesthesiology* 1990; **73**: 532–537.
49. Short L, Hecker RB, Middaugh RE, Menk EJ. A comparison of pulse oximeters during helicopter flight. *Journal of Emergency Medicine* 1989; **7**: 639–643.
50. Silverston P. Pulse oximetry at the roadside: a study of pulse oximetry in immediate care. *British Medical Journal* 1989; **298**: 711–713.
51. Spittal MJ. Evaluation of pulse oximetry during cardiopulmonary resuscitation. *Anaesthesia* 1993; **48**: 701–703.
52. Stewart RD, Paris PM, Winter PM, Pelton GH, Cannon GM. Field endotracheal intubation by paramedical personnel: success rates and complications. *Chest* 1984; **85**: 341–345.
53. Talke P. Measurement of systolic blood pressure using pulse oximetry during helicopter flight. *Critical Care Medicine* 1991; **19**: 934–937.
54. Talke P, Nichols RJ, Traber DL. Monitoring patients during helicopter flight. *Journal of Clinical Monitoring* 1990; **6**: 139–140.
55. Vegfors M, Lennmarken C. Carboxyhaemoglobinaemia and pulse oximetry. *British Journal of Anaesthesia* 1991; **66**: 625–626.
56. Wukitsch MW, Petterson MT, Tobler DR, Pologe JA. Pulse oximetry: analysis of theory, technology and practice. *Journal of Clinical Monitoring* 1988; **4**: 290–301.

British Journal of Anaesthesia 1996; **76**: 731–733

SHORT COMMUNICATIONS

Hydroxyethylstarch compared with modified gelatin as volume preload before spinal anaesthesia for Caesarean section

M. P. VERCAUTEREN, V. HOFFMANN, H. C. COPPEJANS, A. L. VAN STEENBERGE AND H. A. ADRIAENSEN

Summary

We studied 90 patients undergoing elective Caesarean section under spinal anaesthesia who received lactated Ringer's solution 1000 ml with up to 1000 ml of modified gelatin, lactated Ringer's solution 1000 ml with up to 1000 ml of 6% hydroxyethylstarch or only up to 1000 ml of 6% hydroxyethylstarch. Lumbar puncture was performed as soon as 500 ml of the colloid were infused. The incidence of hypotension, number of patients requiring a vasopressor and doses of ephedrine required to restore arterial pressure were significantly lower in favour of those receiving the crystalloid–hydroxyethylstarch combination. In both groups receiving the 2000 ml preload, packed cell volume (PCV) values decreased by more than 20%, which may be of concern in patients already presenting with mild anaemia. In patients who received the colloid without the crystalloid, PCV values decreased by 14% but the risk of severe hypotension was comparable with the crystalloid–gelatin combination. (*Br. J. Anaesth.* 1996; **76**: 731–733)

Key words

Anaesthesia, obstetric. Anaesthetic techniques, subarachnoid. Complications, hypotension. Fluids, i.v.

The risks and benefits of hydration before spinal anaesthesia in obstetrics are subject to much debate. After spinal anaesthesia, even up to 2000 ml of crystalloids may reduce but not eliminate hypotension. During extradural anaesthesia it has been demonstrated that greater volumes of crystalloids (20 ml kg^{-1}) even increase the risk of hypotension compared with lower volumes [1]. This raises doubts, mainly about the usefulness of crystalloid preloading and hydration before (semi-)urgent Caesarean section. However, with colloids, less volumes are required, oncotic pressure may be maintained, but too little attention has been paid to the different properties of the available colloids. The purpose of this study was to compare gelatin with hydroxyethylstarch.

Methods and results

After obtaining approval from the Hospital Ethics Committee and informed consent, we studied 90 term patients presenting for elective Caesarean section, allocated randomly to one of three groups. Sixty patients received lactated Ringer's solution 1000 ml starting in the obstetric ward after which on arrival in the operating theatre they received an additional 16-gauge i.v. cannula for infusion of either modified gelatin (Geloplasma, Merieux, France) or hydroxyethylstarch (HAES-steril 6%, Fresenius, Germany). Another 30 parturients received hydroxyethylstarch 500 ml in the obstetric ward and another 500 ml of the same substance in the operating theatre. Exclusion criteria included patients with pre-eclampsia, hypertension, diabetes, multiple gestation, polyhydramnios, systolic arterial pressure < 100 mm Hg and packed cell volume (PCV) values less than 30% before commencing the anaesthetic technique. Anaesthesia was started during infusion of the second 500-ml volume and comprised a combined spinal–extradural technique using a 26-gauge pencil-point spinal needle (Unisis-corp, Japan). Spinal block was performed with plain bupivacaine 6.6 mg and sufentanil 3.3 µg (i.e. a mixture of 0.5% bupivacaine 2 ml and 1 ml of sufentanil 5 µg ml^{-1}, of which 2 ml were injected) after which an extradural catheter (Perifix Braun, Germany) was inserted for supplementary anaesthesia and relief of postoperative pain. Subsequently, patients were turned to a 15° left lateral tilt. Arterial pressure and heart rate were monitored automatically (Datex AS/3, Helsinki, Finland) every 2.5 min. Ephedrine (5-mg increments) was given when systolic arterial pressure (SAP) decreased to less than 100 mm Hg or to more than 25% (compared with baseline values or at two consecutive measurements), heart rate increase of decreased by 25% (from baseline or at two consecutive measurements) but also in the event of nausea/vomiting or any sense of fainting or non-well-being, even without evidence of haemodynamic instability.

The amount of colloid administered at the moment of spinal injection was recorded. After infusion of 1000 ml of the colloid, a venous blood sample was obtained to measure PCV for comparison with the preoperative value. Measurements and therapy were performed by an anaesthetist unaware of the design of the study.

M. P. VERCAUTEREN, MD, PHD, V. HOFFMANN, MD, H. C. COPPEJANS, MD, A. L. VAN STEENBERGE, MD, H. A. ADRIAENSEN, MD, PHD, Department of Anaesthesiology, University Hospital Antwerp, Wilrijkstraat 10, B-2650 Edegem, Belgium. Accepted for publication: January 5, 1996.

Table 1 Preloading, anaesthetic and hypotensive data (mean (SEM) or number). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with the lactated Ringer's (LR)–HES 6 % group

	LR–gelatin ($n = 30$)	LR–HES 6 % ($n = 30$)	HES 6 % ($n = 30$)
Colloid preload (ml)	913.3 (72.2)	756.7 (45.6)	853.1 (33.1)
Height of block (dermatomes > T7)	4.7 (0.4)	4.8 (0.4)	4.3 (0.5)
Lowest SAP (mm Hg	100.5 (3.7)	108.2 (2.7)	94.1 (3.7)*
SAP < 100 mm Hg (*n*)	18*	8	16*
SAP < 90 mm Hg (*n*)	10*	3	12*
Ephedrine dose (mg)	7.6 (1.5)**	2.5 (0.8)	6.2 (1.5)*
Preoperative PCV (%)	35.2 (0.8)	35.5 (0.85)	34.9 (0.6)
PCV after colloid 1.0 litre	28.1 (0.6)	27.9 (0.75)	30.07 (0.6)*
Decrease in PCV (%)	20.3 (1.2)	21.9 (1.1)	14.2 (1.0)***

Data are expressed as mean (SEM). Statistical analysis was performed with the unpaired, two-tailed Student's *t* test for parametric and the Fisher's exact test for non-parametric data (Macintosh IIsi, StatView II). $P < 0.05$ was considered significant.

There were no differences between the groups in age mean 29.4 (range 25–44), 30.1 (23–42) and 29.2 (20–44) yr), weight (81 (SD 14), 75 (16) and 78 (17) kg) or duration of pregnancy (38.0 (1.5), 38.2 (0.5) and 37.8 (2.6) week). All procedures were uneventful and the mean upper sensory level, determined with an ether swab, reached T2–3 in all groups (table 1). Extradural supplementation was not necessary before delivery in any patient. Severe hypotension (< 90 mm Hg) was noted in one of 10 patients in the lactated Ringer's–HES group compared with at least one of three patients in the lactated Ringer's–gelatin and HES groups ($P < 0.05$). Ephedrine was required less frequently $P < 0.05$) in the lactated Ringer's–HES group (11 patients *vs* 22 patients and 20 patients in the lactated Ringer's-gelatin and HES groups, respectively). As a consequence, the mean dose requirement of ephedrine was also lower in the former group. The mean lowest recorded systolic arterial pressure was higher in lactated Ringer's–HES treated patients but this was significant only compared with the group receiving HES alone ($P < 0.05$) in which hypotension occurred more abruptly.

PCV values in the groups receiving 2000 ml of preload revealed a decrease of 20.3 % and 21.9 %, respectively, whereas with 6 % HES alone it was 14.2 % ($P < 0.001$ compared with the lactated Ringer's–HES group). In none of the parturients was there evidence of respiratory or cardiac problems suggesting fluid overload.

All neonates had Apgar scores greater than 8 at 1 and 5 min and weighed more than 2800 g (mean weight 3170 (range 2820–3360) g, 3180 (2850–3340) g and 3210 (2800–3410) g).

Comment

This study demonstrated that volume preloading is worthwhile if the correct regiment is selected. Our finding that approximately 10 ml kg^{-1} of a colloid or 1000 ml of lactated Ringer's solution with modified gelatin was inadequate to increase the incidence of hypotension may cast doubt on the benefit of hydration compared with no volume treatment. As demonstrated recently, the use of 1000 ml of crystalloids alone did not appear to be better than preloading with only 200 ml [2]. The incidence of hypotension (< 90 mm Hg in one of three patients) was comparable with our results in the groups receiving gelatin with crystalloids or HES alone, although in the study of Jackson, Reid and Thorburn, extremely high doses (up to 50 mg) of ephedrine were required. In the present study in which therapy was started earlier, ephedrine requirements were significantly lower.

In addition to the lack of apparent haemodynamic benefit, volume preloading may have several other disadvantages. The risk of pulmonary oedema, as a result of accumulation of extravascular lung water, may be reduced by the use of colloids as these maintain the oncotic pressure of plasma. Efforts to increase placental blood flow may be counteracted partly by haemodilution. Marked decreases in PCV values decrease the oxygen-carrying capacity of maternal blood. If additional hypotension still occurs despite high preloading volumes, as with the crystalloid–gelatin combination, fetal oxygenation may be seriously compromised.

However, compared with crystalloids, the properties of the available colloids may differ considerably. Hydroxyethylstarch may offer several advantages such as venous thrombosis prophylaxis and an allergic potential which is seven times lower (1/2100) than that of the gelatins [3]. Even in concentrations of 10 % it seems to be safe for the neonate as placental transfer in a sheep preparation has been found to be almost negligible [4]. The 6 % concentration may be preferable in obstetric practice as, compared with the 10 % concentration, its volume retaining effect in excess of 100 % lasts only 30 min which is ideal to cover the interval between administration and delivery. Although hydroxyethylstarch costs twice as much as gelatin, it is six times less expensive than human plasma proteins.

Although we were able to maintain the most optimal haemodynamic stability with the crystalloid–HES combination, our findings were not different from the results of Jackson, Reid and Thorburn [2]. We confirmed that high volumes, even containing gelatins, may not prevent cardiovascular instability, but we suggest that more attention should be paid to the choice of the regimen, colloid, or both. Recently, another study confirmed the superiority of a crystalloid–HES combination compared with crystalloids alone [5]. After intrathecal injection of 0.75% hyperbaric bupivacaine 12 mg, the incidence of hypotension was 45% in those receiving the combination of 500 ml 6% HES and lactated Ringer's solution 1000 ml which was significantly lower than the 85% incidence in the group receiving 2000 ml of crystalloid alone.

We agree with the advice of Rocke and Rout [6] that hydration should not be abandoned routinely without additional studies. We would be interested to know the haemodynamic safety of the high preload used in the present study and the effect of colloids alone combined with the preventive use of vasopressor increments.

References

1. Carvalho C, Mathias R, Senra W, Torres M, Adam C, Vasconcelos A, Moreas J, do Amaral R. Maternal, fetal and neonatal consequences of acute hydration during epidural anesthesia for cesarean section. *Regional Anesthesia* 1993; **18**: 19.
2. Jackson R, Reid JA, Thorburn J. Volume preloading is not essential to prevent spinal-induced hypotension at Caesarean section. *British Journal of Anaesthesia* 1995; **75**: 262–265.
3. Laxenaire M, Charpentier C, Feldman L. Réactions anaphylactoïdes aux substituts colloïdaux du plasma: incidence, facteurs de risque, mécanismes. Enquête prospective, multicentrique française. *Annales Françaises d'Anesthésie et Reanimation* 1994; **13**: 301–310.
4. Marcus M, Vertommen J, Van Aken H. Hydroxyethyl starch versus lactated Ringer's solution in the chronic maternal–fetal sheep preparation: a pharmacodynamic and pharmacokinetic study. *Anesthesia and Analgesia* 1995; **80**: 949–954.
5. Riley ET, Cohen SE, Rubenstein AJ, Flanagan B. Prevention of hypotension after spinal anaesthesia for cesarean section: six percent hetastarch versus lactated Ringer's solution. *Anesthesia and Analgesia* 1995; **81**: 838–842.
6. Rocke DA, Rout CC. Volume preloading, spinal hypotension and Caesarean section. *British Journal of Anaesthesia* 1995; **75**: 257–259.

British Journal of Anaesthesia 1996; **76**: 734–736

Hypotension during subarachnoid anaesthesia: haemodynamic effects of colloid and metaraminol

L. A. H. CRITCHLEY AND F. CONWAY

Summary

We have studied 45 patients, aged 60–95 yr, receiving subarachnoid block for neck of femur fractures. Patient received either colloid (polygeline, Haemaccel) 8 ml kg^{-1} ($n = 15$), metaraminol 5 µg kg^{-1} and 1.7 µg kg^{-1} min^{-1} ($n = 15$) or a combination of both treatments to maintain systolic arterial pressure (SAP) between 75 and 100% of baseline. If necessary, additional colloid 2×4 ml kg^{-1} or metaraminol 3×2.5 µg kg^{-1} was given. Arterial pressure was measured by automated oscillotonometry, central venous pressure (CVP) by a manometer and cardiac index (CI), stoke index (SI) and heart rate (HR) by transthoracic electrical bioimpedance. Systemic vascular resistance index (SVRI) was derived. Colloid was less effective than metaraminol ($P < 0.05$). In the colloid group, SAP and SVRI decreased and CVP, CI and SI increased ($P < 0.001$). In the metaraminol group, initial decreases in SAP, SVRI and CVP were restored after 10–15 min and HR decreased after 12 min ($P < 0.001$). In the combined group, initial decreases in SAP and SVRI were restored after 4 and 16 min, and CVP, CI, SI and HR increased ($P < 0.001$). Metaraminol was more effective than colloid because it increased SVRI, whereas colloid increased CVP without significantly increasing CI. (*Br. J. Anaesth.* 1996; **76**: 734–736)

Key words

Anaesthetic techniques, subarachnoid. Complications, hypotension. Measurement techniques, transthoracic electrical impedance. Fluids, i.v. Sympathetic nervous system, metaraminol.

Hypotension is a common problem during subarachnoid block and elderly patients are particularly at risk. Different views exist on how this hypotension should be managed [1]. There are few data on the elderly, and only the effects of crystalloid preloading and the use of ephedrine have been investigated [2, 3]. Recently, we showed that i.v. fluids and ephedrine were not always effective in preventing hypotension during subarachnoid block in the elderly and we suggested that treatment with a predominantly alpha adrenergic receptor agonist would be more effective [4]. In the present study, we have compared the haemodynamic effects during subarachnoid block of colloid solution and the alpha agonist metaraminol.

Methods and results

After obtaining local Ethnics Committee approval and written informed consent, we studied 45 ASA II and III Chinese patients undergoing surgical fixation of fractured neck of femur. Oral diazepam 5–10 mg was given 1 h before surgery. Subarachnoid block was performed using 0.5% bupivacaine 2.5–3.0 ml (Marcain Spinal 0.5% Heavy, Astra). We measured systolic (SAP) and mean (MAP) arterial pressures using automated oscillotonometry, central venous pressure (CVP) using a manometer and cardiac index (CI), stroke index (SI) and heart rate (HR) by transthoracic electrical bioimpedance using the BoMed NCCOM3-R7S (BoMed Medical Manufacturing Ltd, Irvine, CA, USA). We derived systemic vascular resistance index (SVRI). Data were collected at 1-min intervals (5-min intervals for CVP) for 3–5 min before and 0–25 min during subarachnoid block. For a more detailed description of our methodology, see previous publications [4, 5].

Patients were allocated to one of three regimens to prevent hypotension using block randomization with sequentially numbered sealed forms. Immediately after subarachnoid block, group I received a rapid infusion of colloid 8 ml kg^{-1} (3.5% polygeline, Haemaccel, Behringwerke, Germany), group II received an initial bolus of metaraminol 5 µg kg^{-1} followed by an infusion of 1.7 µg kg^{-1} min^{-1} and group III received both colloid and metaraminol. Rescue treatment was given if SAP decreased to less than 75% of baseline on two consecutive occasions. Group I received a rapid infusion of colloid 4 ml kg^{-1} and, if necessary, repeated once to restore SAP. If hypotension persisted, metaraminol was given, as per group II. Groups II and III received up to three boluses of metaraminol 2.5 µg kg^{-1} to restore SAP. If hypotension persisted, colloid 8 ml kg^{-1} was given.

Continuous haemodynamic data were analysed at 1-min intervals. Percentage changes compared with baseline were also calculated at 1-min intervals and their means compared. Numerical differences were used for CVP. Student's *t* test, analysis of variance

---

LESTER A. H. CRITCHLEY, BMEDSCI, MB, CHB, FFARCSI, FRANCES CONWAY*, MB, BCH, FFARCSI, Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong. Accepted for publication: December 12, 1995.

*Present address: St Vincent's Hospital, Merrion Road, Dublin, Ireland.

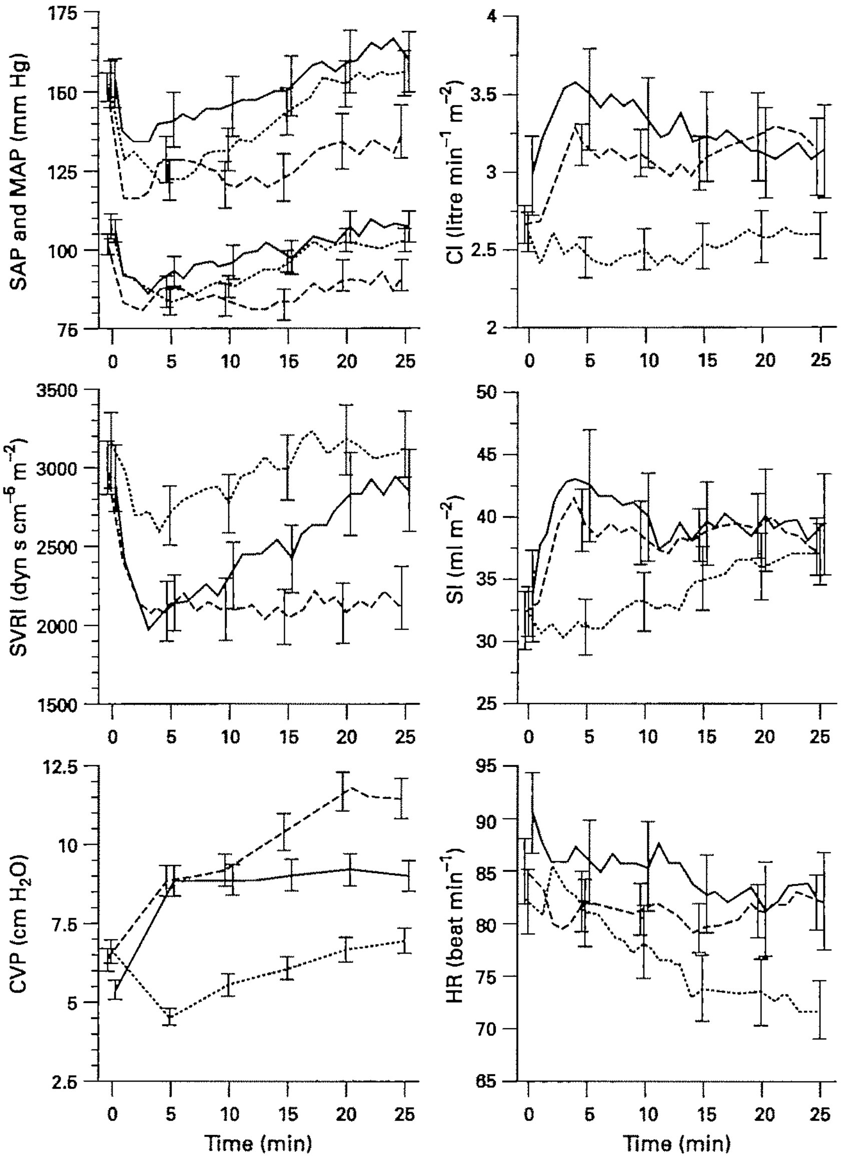


Figure 1 Mean (SEM) haemodynamic variables at baseline (0 min) and during the first 25 min of subarachnoid block for all patients in the three treatment groups: —— = colloid alone; ---- = metaraminol alone; and —— = metaraminol with colloid.

for factors and repeated measures and chi-square test were used for statistical analysis. $P < 0.05$ was considered significant and results are given as mean (SD or range). The power of the study was assessed using Altman's method [6]. Fifteen patients per group were required to detect changes of less than 10% between haemodynamic data.

We studied 11 male and 34 female patients, aged 78 (60–95) yr, weight 48 (7) kg and height 154 (8) cm. Maximum sensory level in pinprick was thoracic dermatome 6 (1–11). Patient characteristics, maximum sensory level and baseline haemodynamic data were similar in the three treatment groups. The colloid regimen failed to maintain an adequate SAP on eight occasions. The metaraminol regimen failed significantly less often ($P < 0.05$), once in group II and once in group III, and resulted in an excessive SAP in four patients in group II and six patients in group III.

Haemodynamic changes after subarachnoid block are shown in figure 1. In the colloid group, significant decreases in SAP, MAP and SVRI and increases in CVP, CI and SI occurred ($P < 0.001$). These changes were significant ($P < 0.05$) after 1 min for SAP, MAP and SVRI, after 5 min for CVP and after 2 min for CI and SI. There was no significant change in HR. In the metaraminol group, significant decreases in SAP, MAP, SVRI, CVP and HR occurred ($P < 0.001$). These changes were significant ($P < 0.05$) at 1–14 min for SAP, at 1–15 min for MAP, at 2–10 min for SVRI, at 5–10 min for CVP and at 12–25 min for HR. There were no significant changes in CI or SI. In the combined group there were significant decreases in SAP, MAP, SVRI and HR, and increases in CVP, CI and SI ($P < 0.001$). These changes were significant ($P < 0.05$) at 1–4 min for SAP, at 1–10 min for MAP, at 1–16 min for SVRI, after 5 min for CVP, after 2 min for CI and SI, and after 14 min for HR.

The magnitude of the haemodynamic effects of the three treatments during subarachnoid block are shown in table 1. Where treatment was effective,

Table 1 Percentage changes (Δ) or numerical differences (Diff.) (mean (SD)) compared with baseline values for haemodynamic variables, for the established effects of subarachnoid block when treatment was successful in the three treatment groups (15–25 min) and when treatment was unsuccessful in the colloid group (10–15 min). SAP = Systolic arterial pressure, MAP = mean arterial pressure, SVRI = systemic vascular resistance index, CVP = central venous pressure, CI = cardiac index, SI = stroke index and HR = heart rate. $^*P < 0.05$, $^{**}P < 0.01$ compared with baseline

			Colloid	
	Metaraminol ($n = 14$)	Combined ($n = 14$)	(Successful) ($n = 7$)	(Unsuccessful) ($n = 8$)
ΔSAP (%)	2 (13)	6 (14)	−9 (7)*	−31 (6)**
ΔMAP (%)	−3 (11)	1 (10)	−11 (9)*	−29 (5)**
ΔSVRI (%)	−2 (16)	−2 (28)	−20 (12)**	−38 (12)**
Diff. CVP (cm H_2O)	0.2 (2.6)	3.4 (3.1)**	2.5 (2.6)*	4.5 (3.7)**
ΔCI (%)	0 (15)	5 (18)	11 (14)	12 (17)
ΔSI (%)	14 (22)*	17 (19)**	13 (15)	26 (25)*
ΔHR (%)	−11 (12)**	−10 (8)**	−2 (5)	−10 (8)**

percentage changes were averaged between 15 and 25 min, and where additional colloid failed between 10 and 15 min.

Comment

Current clinical practice is to use crystalloid, up to 2 litre, before and during subarachnoid block to prevent hypotension [1]. In the present study, we used colloid solution during the onset phase of subarachnoid block. This practice prevents excessive increases in CVP (table 1) and reduces the fluid volume required [4]. However, we found that even large volumes of colloid, up to 16 ml kg^{-1}, failed to correct hypotension in more than 50% of our patients. Coe and Revanas [2] reported similar findings in patients with a high subarachnoid block (above T7) after preloading with crystalloid 16 ml kg^{-1}. In fact, administration of colloid appeared to decrease SVRI and yet cardiac output did not increase significantly despite increases in CVP, suggesting that elderly patients have a reduced ability to respond to i.v. fluids (table 1, fig. 1).

In the present study, metaraminol was effective at maintaining SAP during subarachnoid block in 93% of patients, the principal action of metaraminol being to maintain SVRI (table 1). However, metaraminol caused excessive treatment in some patients (33%). In these patients subarachnoid block may have caused only a small decrease in SAP and the use of prophylactic treatment may have been unnecessary. CVP during high subarachnoid block decreases by 2.5 (1.5) cm H_2O [5]. Metaraminol prevented this decrease (table 1), suggesting that metaraminol also acts by venoconstricting capacitance vessels. However, CVP did not increase sufficiently to increase cardiac output.

Ephedrine is the most frequently studied vasopressor during subarachnoid block. Comparing the present data with data from our previous study [4], we found ephedrine to be less effective than metaraminol at maintaining SVRI and that part of its action was to increase cardiac output and HR. Also, the efficacy of ephedrine depended on maintaining the patient well hydrated with i.v. fluids. In comparison, metaraminol was much less dependent on i.v. fluids.

Administration of i.v. fluids during subarachnoid block is important, because it maintains preload and cardiac output. However, the use of large volumes of fluid to increase preload sufficiently to raise cardiac output and SAP is not always successful in the elderly patient. Therefore, this practice should not be encouraged because of the risk of fluid overload. Hypotension may be treated more effectively by using a vasopressor and we found that infusion of metaraminol was highly effective because it acted by increasing systemic vascular resistance.

References

1. McCrae AF, Wildsmith JA. Prevention and treatment of hypotension during central neural block. *British Journal of Anaesthesia* 1993; **70**: 672–680.
2. Coe AJ, Revanas B. Is crystalloid preloading useful in spinal anaesthesia in the elderly? *Anaesthesia* 1990; **45**: 241–243.
3. Hemmingsen C, Poulsen JA, Risbo A. Prophylactic ephedrine during spinal anaesthesia: double-blind study in patients in ASA groups I–III. *British Journal of Anaesthesia* 1989; **63**: 340–342.
4. Critchley LA, Stuart JC, Conway F, Short TG. Hypotension during subarachnoid anaesthesia: haemodynamic effects of ephedrine. *British Journal of Anaesthesia* 1995; **74**: 373–378.
5. Critchley LA, Stuart JC, Short TG, Gin T. Haemodynamic effects of subarachnoid block in elderly patients: measurement by transthoracic bioimpedance. *British Journal of Anaesthesia* 1994; **72**: 464–470.
6. Altman DG. How large a sample? In: Altman DG, Gore S, eds. *Statistics in Practice*. London: British Medical Association, 1993; 6–8.

British Journal of Anaesthesia 1996; **76**: 737–739

Interference of volatile anaesthetics with infrared analysis of carbon dioxide and nitrous oxide tested in the Dräger Cicero EM using sevoflurane

A. R. WILKES AND W. W. MAPLESON

Summary

In theory, setting an infrared multi-gas analyser to measure a volatile anaesthetic different from that in the sampled gas mixture may cause interference with carbon dioxide and nitrous oxide readings. The theory was investigated during evaluation of the Dräger Cicero EM anaesthetic workstation for the Medical Devices Agency. Interference occurred as predicted, and was most pronounced when the vapour analyser of the Cicero EM was deliberately and erroneously set to measure isoflurane, but with sevoflurane present in the gas mixture. With 6% sevoflurane in the gas mixture, the carbon dioxide reading decreased from 5% to 3.6%, and the nitrous oxide reading increased from 0% to 8% although, as the apparent isoflurane reading was 9%, the Cicero EM would alert the operator to the problem. However, operators are encouraged to ensure that, when using gas analysers such as that incorporated into the Cicero EM, the analyser is set to measure the correct volatile anaesthetic (the Cicero EM does this automatically when a Vapor vaporizer is attached) and the breathing system does not contain any other volatile anaesthetic agents. (*Br. J. Anaesth.* 1996; **76**: 737–739)

Key words

Measurement techniques, spectrophotometry. Anaesthetics volatile. Equipment, gas analysers.

Infrared absorption is a common method of gas analysis for measuring the concentrations of carbon dioxide, nitrous oxide and volatile anaesthetic agents in gas mixtures during anaesthesia. This type of analyser uses different wavelengths of infrared light to determine the concentrations of carbon dioxide, nitrous oxide and volatile anaesthetic; the same wavelength is used for all current volatile anaesthetics, but different sensitivities are set for each agent. Typically, the highest sensitivity is set for halothane and the lowest for sevoflurane. This method of analysis implies that the presence of a volatile anaesthetic different from that set to be measured causes an error in the volatile anaesthetic reading. For example, 1% isoflurane causes an apparent halothane reading of approximately 6% when the analyser is set to measure halothane [1].

Volatile anaesthetics also absorb infrared radiation at the wavelengths used for measurement of carbon dioxide and nitrous oxide. This is corrected by subtracting amounts from the carbon dioxide and nitrous oxide signals appropriate to the volatile anaesthetic being measured and its measured concentration. Therefore, provided the analyser is set to measure the correct anaesthetic, or the analyser detects the particular volatile anaesthetic automatically, the analyser can compensate for this effect. However, if the analyser is set to measure a volatile anaesthetic different from that present in the gas mixture, the wrong corrections are made and the carbon dioxide and nitrous oxide readings are in error.

An opportunity to test this theory occurred during evaluation of the Dräger Cicero EM anaesthetic workstation for the Medical Devices Agency. This anaesthetic workstation incorporates the ANDROS 4610 gas analyser, which is also used in the North American Dräger Narkomed 4 and Vitalert 3000 monitor, and the Drägerwerk PM 8050 monitor. Information provided by the manufacturer stated that the analyser software compensates for the cross-sensitivity of carbon dioxide, nitrous oxide and volatile anaesthetic, so that the displayed concentrations of these gases and vapours are accurate. However, it was found that if the ANDROS 4610 was set deliberately to measure a volatile anaesthetic different from that in the gas mixture being sampled, interference with the carbon dioxide and nitrous oxide readings occurred as predicted. The interference was most pronounced with sevoflurane present in the gas mixture and with the analyser set to measure isoflurane. The extent of the interference was investigated.

Methods and results

Carrier gas (4.95% carbon dioxide/balance nitrogen) (BOC Special Gases) was set at a flow of 2 litre min^{-1} using a RT-200 calibration analyser (Timeter Corp) and was passed through a vaporizer (Sevotec 3, Ohmeda) to add various concentrations of sevoflurane to the gas mixture. A turbine vane transducer cartridge from a 5410 volume monitor (Ohmeda), placed in the gas pathway, was used to ensure that the carrier gas and sevoflurane were mixed thoroughly. The resulting gas mixture was sampled from

---

ANTONY R. WILKES, MSC, MIPEMB, WILLIAM W. MAPLESON, DSC, FINSTP, FIPEMB, Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN. Accepted for publication: December 15, 1995.

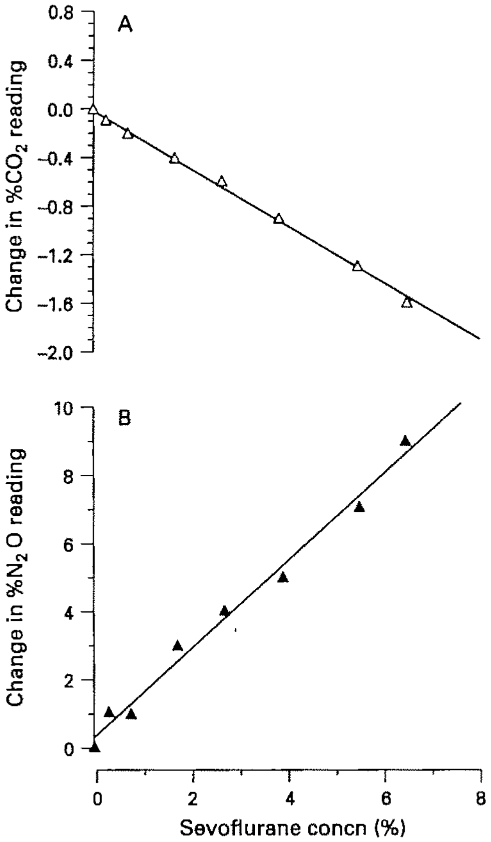


Figure 1 Change in carbon dioxide (CO_2) (A) and nitrous oxide (N_2O) (B) readings, with fitted regression lines, as the Cicero EM is changed from being set to measure sevoflurane to being set to measure isoflurane, against increasing sevoflurane concentration. The changes in the CO_2 and N_2O readings are −0.24% CO_2 and +1.27% N_2O, respectively, for each 1% increase in sevoflurane concentration.

a common sampling point, both by the ANDROS analyser on a Cicero EM anaesthetic workstation (Dräger, Germany) and by an interference refractometer on loan from the National Physical Laboratory [2]. The gas mixture sampled was therefore independent of the breathing system of the Cicero EM. At each vaporizer setting, the analyser was set to measure sevoflurane and the carbon dioxide, nitrous oxide and volatile anaesthetic readings were noted; the analyser was then set to measure isoflurane and the readings repeated. The readings were also logged automatically onto a computer (Apple Macintosh LC475 running Kermit communication software) via the RS232 serial output on the Cicero EM. Changes in the carbon dioxide and nitrous oxide readings were taken to be the difference between the pairs of readings obtained at each vaporizer setting. The actual concentration of sevoflurane in the gas mixture was determined from the refractometer using refractive powers of 1428.6 for sevoflurane, 413.56 for carbon dioxide (at 22 °C and 101.3 kPa [3]) and 282.12 for nitrogen (at 15 °C and 101.3 kPa [4]), assuming that the relative concentrations of carbon dioxide and nitrogen remained the same, and correcting for temperature and pressure [3]. The concentration of carbon dioxide in the carrier gas was also checked with the refractometer.

The carbon dioxide and nitrous oxide readings changed linearly with sevoflurane concentration (fig. 1). The slope of the change in carbon dioxide reading with increasing sevoflurane concentration was −0.24, and that for nitrous oxide, +1.27.

Comment

The International Standard for capnometers (ISO 9918:1993) specifies gas mixtures to be used to determine the interference effect of gases and vapours on the carbon dioxide reading. One such gas mixture specified is 6% sevoflurane in 5% carbon dioxide, balance nitrogen. If the ANDROS analyser in the Cicero EM is set correctly to measure sevoflurane in the gas mixture, then carbon dioxide readings are displayed which are within the tolerance specified in ISO 9918:1993. However, if the analyser is set to measure isoflurane, the carbon dioxide reading decreases with this gas mixture from 5% to 3.6%. Conversely, if isoflurane is present in the gas mixture, and the analyser is set to measure sevoflurane, the carbon dioxide reading increases as the isoflurane concentration increases. The draft International Standard for anaesthetic gas monitors (ISO/DIS 11196) specifies gas mixtures to be used to determine the interference effect on the nitrous oxide reading. Again, if the analyser is set correctly to measure sevoflurane, then the nitrous oxide reading is accurate. However, if the analyser is set to measure isoflurane, and 5% sevoflurane is in the gas mixture (as specified in ISO/DIS 11196), the nitrous oxide reading increases from 0 to 6%.

The Cicero EM detects which vaporizer has been fitted using a coding on the rear of Dräger Vapor 19.n vaporizers and automatically selects the appropriate sensitivity on the gas analyser. Therefore, in normal clinical practice, it would require a deliberate action by the anaesthetist to set the analyser to measure a volatile anaesthetic different from that of the vaporizer on the Cicero EM workstation. Even then, an advisory message is displayed and, if the vaporizer is changed, the setting of the analyser is automatically changed appropriately. Therefore, in the Cicero EM, inappropriate setting of the gas analyser is extremely unlikely. However, when that analyser (or any other analyser working on the same principle) is used in isolation (as was effectively the case in these experiments), the correct setting of the anaesthetic to be measured is dependent on the operator.

In addition, the volatile anaesthetic in use is absorbed into the walls of the breathing system [5, 6]. During subsequent use with a different anaesthetic, the anaesthetic used previously desorbs from the breathing system and is present in the gas sampled by the analyser, causing interference. Using a low-flow system exacerbates this effect.

Whatever the circumstances—whether the analyser is set to measure the wrong volatile anaesthetic or the sample from the breathing system contains an additional, "foreign", agent—the displayed concentration of the volatile is the concentration used to correct the carbon dioxide and nitrous oxide readings. However, any error in the reading for the volatile anaesthetic is likely to be more important clinically than the resulting error in carbon dioxide or nitrous oxide. Nevertheless, it is important to be aware that the carbon dioxide and nitrous oxide readings are also in error.

The Dräger Cicero EM incorporates a sophisticated and generally accurate gas analyser. However, when using this, or a similar gas analyser, operators should check that the analyser has been set to measure the correct anaesthetic, and should be vigilant that the breathing system does not contain a mixture of volatile anaesthetics. Failure to do so could cause interference with the carbon dioxide and nitrous oxide readings and also give a false reading for the volatile anaesthetic.

References

1. Guyton DC, Gravenstein N. Infrared analysis of volatile anesthetics: impact of monitor agent setting, volatile mixtures, and alcohol. *Journal of Clinical Monitoring* 1990; **6**: 203–206.
2. Downs MJ, Birch KP. Bi-directional fringe counting interference refractometer. *Precision Engineering* 1983; **5**: 105–110.
3. Allison JM, Gregory RS, Birch KP, Crowder JG. Determination of anaesthetic agent concentration by refractometry. *British Journal of Anaesthesia* 1995; **74**: 85–88.
4. Birch KP. Precise determination of refractometric parameters for atmospheric gases. *Journal of the Optical Society of America A* 1991; **8**: 647–651.
5. Targ AG, Yasuda N, Eger EI II. Solubility of I-653, sevoflurane, isoflurane and halothane in plastics and rubber composing a conventional anesthetic circuit. *Anesthesia and Analgesia* 1989; **69**: 218–225.
6. Gilly H, Weindlmayr-Goettel M, Köberl G, Steinbereithner K. Anaesthetic uptake and washout characteristics of patient circuit tubing with special regard to current decontamination techniques. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 621–627.

British Journal of Anaesthesia 1996; **76**: 740–743

CASE REPORT

Use of recombinant human erythropoietin to facilitate liver transplantation in a Jehovah's Witness

N. J. SNOOK, H. A. O'BEIRNE, S. ENRIGHT, Y. YOUNG AND M. C. BELLAMY

Summary

A 46-yr-old woman with rapidly progressing primary biliary cirrhosis presented for liver transplantation. The use of preoperative recombinant human erythropoietin enabled this to be achieved without prohibited blood products. Perioperative management of this patient and general principles of management of Jehovah's Witnesses undergoing major surgery are discussed. (*Br. J. Anaesth.* 1996; **76**: 740–743)

Key words
Liver, transplantation. Blood, erythropoietin. Complications, Jehovah's Witness.

Patients who are Jehovah's Witnesses are unable, for religious reasons, to accept blood (including predonated autologous blood) and several blood products. Major surgery in these patients is therefore challenging both to the surgeon and anaesthetist. Liver transplantation represents the acme of major surgery with considerable potential for blood loss. It involves division and re-anastomosis of major vessels, including the vena cava, is performed in patients with underlying liver disease and involves removal of the liver (anhepatic period) with a consequent obligatory coagulopathy and fibrinolytic tendency.

Case report

a 46-yr-old female Jehovah's Witness presented to the regional hepatology unit with a 4-yr history of lethargy and pruritis, and a 1-yr history of jaundice. She was tea-total and otherwise healthy with no past medical history of note. On examination she was icteric (serum bilirubin 51 μmol litre^{-1}) and well nourished. An increased anti-mitochondrial antibody titre was detected. Abdominal computed tomography and bone scan were normal. Magnetic resonance imaging was consistent with cirrhosis. A diagnosis of primary biliary cirrhosis was made. In view of the patient's religious beliefs no liver biopsy was performed because of the risk of bleeding.

At this time, liver synthetic function was relatively good, with a prothrombin time (PT) of 12 s and a serum albumin concentration of 30 g litre^{-1}. She therefore presented a dilemma. Her state of health at presentation placed her in a low-risk group for liver transplantation. With this clinical picture she could be expected to enjoy 2 yr of reasonable quality life before end-stage liver failure developed and therefore she did not need urgent transplantation. Waiting for end-stage disease, however, would imply deteriorating clotting function and general metabolic reserve, hence liver transplantation would be more hazardous. During counselling, expected disease progression, prognosis and treatment options were explained. After discussion with hepatologists, surgeons, anaesthetists and the Jehovah's Witness Hospital Liaison Committee, the patient decided to accept liver transplantation.

A blood products regimen acceptable to both the patient and the Jehovah's Witness Hospital Liaison Committee was established. This precluded transfused bank blood (either homologous or autologously pre-donated) and fresh frozen plasma. Platelets, factor concentrates, human albumin and modified fluid gelatin (Gelofusine) were allowed under the regimen. Continuous circuit cell salvage and reinfusion whereby scavenged blood was maintained in continuity with the patient's circulation was also permitted.

At the time of consideration for transplantation, haemoglobin concentration was 11.1 g dl^{-1}. Vitamin B_{12} and folate concentration were within the reference range. Human recombinant erythropoietin therapy (r-HuEPO) was commenced at a dose of 2000 iu s.c. for 5 days in every 7. Ferrous sulphate supplementation was given daily.

During r-HuEPO therapy she was reviewed initially twice weekly, then weekly to monitor treatment. Apart from mild headaches experienced in the first week of treatment, there were no other side effects. Hypertension was not observed.

Figure 1 shows the increase in haemoglobin concentration after commencement of r-HuEPO. Erythropoietin dose was reduced in 1000 iu day^{-1} when haemoglobin concentration reached 14 g dl^{-1} after 5 weeks of treatment. The patient was then scheduled for liver transplantation.

NICOLA J. SNOOK, MB, CHB, FRCA, HUGH A. O'BEIRNE, MB, BCH, BAO, FFARCSI, SIMON ENRIGHT, MB, CHB, FRCA, YATIN YOUNG, MRCP, FRCA, MARK C. BELLAMY, MA, MB, BS, FRCA, Intensive Care Unit, St James's University Hospital, Beckett Street, Leeds LS9 7TF. Accepted for publication: December 14, 1995.

Correspondence to M. C. B.

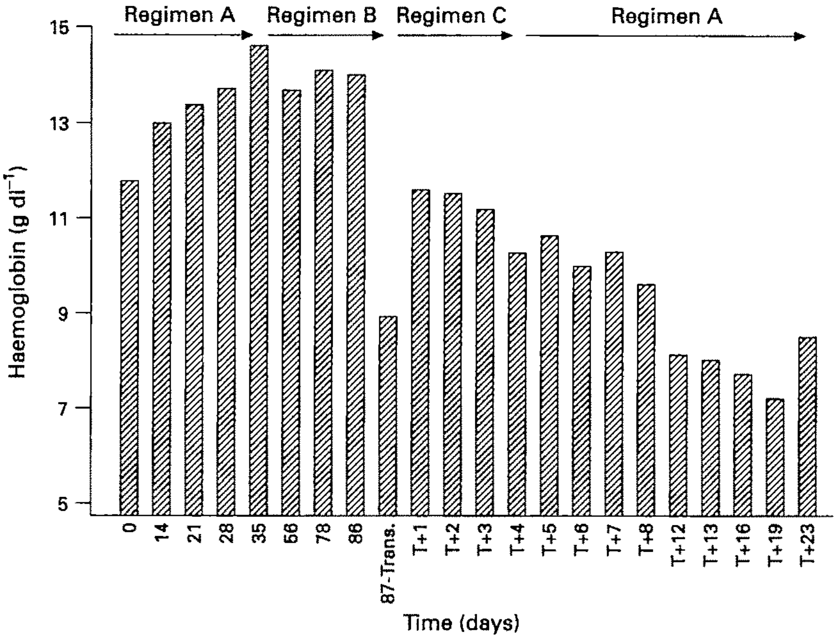


Figure 1 Increase in haemoglobin concentration in the liver transplant Jehovah's Witness after commencement of recombinant human erythropoietin treatment.

PEROPERATIVE MANAGEMENT

Twelve weeks after commencing erythropoietin, a suitable liver became available. The patient was admitted to hospital and prepared for theatre. Non-invasive monitoring was commenced and anaesthesia induced with midazolam 7.5 mg, alfentanil 7.5 mg and atracurium 50 mg. After tracheal intubation, the lungs were ventilated with desflurane in oxygen-enriched air. Anaesthesia was supplemented with alfentanil 3 mg h^{-1} and neuromuscular block was produced with atracurium 0.5 mg kg^{-1} h^{-1} [1]. Additional monitoring included a triple-lumen central venous catheter, mixed venous oximetric right-ejection fraction pulmonary artery flotation catheter, and a radial arterial cannula. An 18-French gauge percutaneous cardiac bypass cannula was inserted into the internal jugular vein and connected to a rapid infusion system (RIS) (Hemonetics, Braintree, MA, USA) [2]. This is standard practice for liver transplantation and provides access for venovenous bypass and rapid infusion of fluids (up to 1500 ml min^{-1}) in the event of acute loss. In this case only salvaged blood (infused in continuity with the patients circulation), crystalloid or colloid was used. An 18-French gauge bypass cannula was inserted surgically into the right femoral vein to allow venovenous bypass [3]. Dopamine 3 μg kg^{-1} min^{-1} and 4 % glucose in 0.18 % saline (70 ml h^{-1}) infusions were commenced and continued into the post-operative period according to our regimen [4].

An inverse-T abdominal incision was made. During the dissection phase (I), meticulous surgical haemostasis was achieved using argon beam coagulation. All bleeding was scavenged to a cell saver [5] and immediately washed and reinfused by RIS. This enabled salvaged cells to remain in continuity with the circulation. The liver showed early cirrhosis. Primary biliary cirrhosis was later confirmed on histology.

Coagulation was monitored using PT, activated partial thromboplastin time, thrombin time, fibrinogen concentration, platelet count and thrombelastography [6, 7]. At the beginning of the anhepatic phase (II) a bolus dose of tranexamic acid 1000 mg was given and an infusion commenced to prevent fibrinolysis. This dose has been found to reduce blood loss by 50 % [8, 9].

Haemoglobin concentration decreased from 10.7 g dl^{-1} in phase I to 8.9 g dl^{-1} in phase III. Much of this reduction resulted from aggressive haemodilution with colloid during phase I. Cryoprecipitate and platelets (8 u.) were administered after reperfusion. A total of 800 ml of salvaged blood was reinfused. Remaining fluid replacement consisted of modified fluid gelatin 3329 ml.

Surgery was completed uneventfully. After tracheal extubation in the operating theatre, the patient was transferred to the intensive care unit for overnight observation. Postoperative haemoglobin concentration was 10.8 g dl^{-1}, necessitating prophylactic venesection before discharge to the liver unit [10].

On the second day after operation, the patient developed an increased PT (99 s), oliguria and metabolic acidosis. Hepatic angiography and Doppler studies excluded a diagnosis of hepatic artery thrombosis. A provisional diagnosis of primary non-function was made [11]. Management was conservative, with venovenous haemodiafiltration (CVVHD) to control acidosis. Spontaneous improvement of PT forestalled listing for re-transplantation. Over the next 5 days, urine output improved and CVVHD was discontinued. During this time haemoglobin concentration remained stable at 8.4 g dl^{-1}. After another 10 days, erythropoietin was reduced to 1000 iu on alternate days and she was discharged home, exactly 1 month after transplantation.

At the 6-month follow-up she remained well, with a haemoglobin concentration of 11.5 g dl^{-1}. Her liver function tests had improved compared with results at hospital discharge (shown in parentheses): bilirubin 10 (44) µg ml, ALT 63 (96) iu ml^{-1} ALP 446 (629) iu ml^{-1} albumin 43 (37) g ml^{-1}.

Discussion

We have described a case of liver transplantation in a Jehovah's Witness when preoperative recombinant human erythropoietin was used to avoid perioperative blood transfusion. There is one previous description in the literature of liver transplantation in Jehovah's Witnesses [12]. This article was interesting both for its financial conclusions and the acceptance of plateletpheresis. This demonstrates the variability between different groups of Jehovah's Witnesses in their beliefs, and the importance of consulting Liaison Committees.

Jehovah's Witnesses present a special clinical and ethical problem. They believe that blood transfusion is forbidden and use scriptural passages in support of this view: "only flesh with its soul—its blood you must not eat" (Genesis 9: 3–4), "you must pour its blood out and cover it with dust" (Leviticus 17: 13–14), "abstain from fornication and from what is strangled and from blood" (Acts 15: 19–21) [13]. Jehovah's Witnesses will not accept red blood cells, whole blood, plasma, white cells and usually platelets. This includes pre-donation and transfusion with autologous blood, believing any blood removed from the body should be destroyed. Uninterrupted intraoperative cell salvage systems are accepted by some individuals, as are immunoglobulins, albumin and clotting factor concentrates. Consultation with the local advisory body is therefore essential to establish individual beliefs and wishes. Witnesses will accept solid organ donation.

Major surgery on Jehovah's Witnesses requires careful planning and of all procedures liver transplantation is the most hazardous [12]. Bontempo, Lewis and Van Thiel quote median red blood cell transfusion requirements of 10 u. in an unselected liver transplant population [14] (although in some cases it greatly exceeded this value). Improvements in surgical haemostasis using argon beam coagulators, cell salvage and improved understanding of coagulopathy and fibrinolysis [9] have reduced demand for red cells, but transfusion-free liver transplantation still presents a major challenge.

Timing of the procedure was crucial. In our centre, patients presenting with primary biliary cirrhosis are usually considered for transplantation only when serum bilirubin concentration exceeds 100 µmol litre^{-1} and hepatic synthetic function is impaired. Associated coagulopathy however could have increased the perioperative risk. A decision to offer transplantation relatively early in the clinical course was therefore made.

In anticipation of major blood loss, we decided to increase our patient's haemoglobin concentration to the highest preoperative value safely achievable. Erythropoietin is a circulating glycosylated polypeptide. Recombinant human erythropoietin (r-HuEPO; manufactured using Chinese hamster ovarian cell lines) acts on bone marrow selectively to stimulate erythropoiesis. This leads to an increased packed cell volume (PCV) and reticulocyte count. Side effects reported include allergic reactions, hypertension and convulsions. Iron deficiency is prevented with supplementation [15].

Erythropoietin has been used to facilitate autologous blood transfusion before elective surgery [16]. Its use in Jehovah's Witnesses has been reported widely. Koestner and co-workers [17] first used it in 1990 to treat severe anaemia in a major trauma victim, increasing PCV from 15% to 30% after 18 days. Since then it has been used to treat a child with resistant anaemia [18] and before operation in patients requiring cardiac surgery [19].

Our patient's haemoglobin concentration increased from 11.8 to 14.1 g dl^{-1} over 11 weeks. The intraoperative reduction by 4 g dl^{-1} to 10.7 g dl^{-1} was more manageable than a predicted reduction to 6 g dl^{-1} had no measures been taken before operation. Treatment with r-HuEPO was without adverse effects.

During operation we aimed to minimize blood loss and maximize cell salvage by limiting the use of laparotomy swabs within the operative field. Aggressive early haemodilution reduced the cell content of shed blood. Optimizing coagulation was imperative and based predominantly on thrombelastography. Although other centres have used plateletpheresis [12] more on an economic basis than clinical need, our patient had decided to accept platelets which she received on graft reperfusion. During the anhepatic and reperfusion stages of transplantation, there is an imbalance between the activators and inhibitors of fibrinolysis leading to activation of fibrin and an increase in fibrinolysis. This imbalance can be redressed pharmacologically with tranexamic acid which was administered prophylactically during the anhepatic phase at this has been shown to decrease overall blood loss by 50% [8, 9].

Blood conservation continued into the postoperative period. Chernow [20] demonstrated that iatrogenic anaemia caused by overzealous blood sampling is reduced by microchemistry (restricting samples to a maximum of 4 ml per day) and limiting line dead-space, allowing all haemotological and biochemical analyses.

Primary non-function of the liver occurs in up to 10% of cases. This is usually associated with preservation injury [21]. It is relatively uncommon with short preservation times in well-perfused grafts, so it is surprising that primary non-function occurred in this case. Fortunately, it was self-limiting and did not necessitate regrafting. This could have been associated with poor outcome.

References

1. Miller RD. Pharmacokinetics of atracurium and other non-depolarizing neuromuscular blocking agents in normal patients and those with renal or hepatic dysfunction. *British Journal of Anaesthesia* 1986; 58 (Suppl. 1): 11S–13S.
2. Sassano JJ. The rapid infusion system. In: Winter PM, Kang

YG, eds. *Hepatic Transplantation: Anaesthetic and Perioperative Management.* New York: Praeger, 1986; 120–134.

3. Shaw BW jr, Martin DJ, Marquez JM, Kang YG, Bugbee AC jr, Iwatsuki S, Griffith BP, Hardesty RL, Bahnson HT, Starzl TE. Venous bypass in clinical liver transplantation. *Annals of Surgery* 1984; **200**: 524–534.
4. Webster NR, Bellamy MC, Sadek SA, Lodge JPA. Right ventricular function in orthotopic liver transplantation: a comparison of two anaesthetic techniques. *British Journal of Anaesthesia* 1994; **72**: 418–421.
5. Lindop MJ, Farman JV, Smith MF. The Cambridge–King's College Hospital Series. In: Calne RY, ed. *Liver Transplantation.* New York: Grune and Stratton, 1983; 128–129.
6. Mallett SV, Cox DJA. Thrombelastography. *British Journal of Anaesthesia* 1992; **69**: 307–313.
7. Kang YG, Martin DJ, Marquez JM, Lewis JH, Bontempo FA, Shaw BW jr, Starzl TE, Winter PM. Intra-operative changes in blood coagulation and thromboelastographic monitoring in liver transplantation. *Anesthesia and Analgesia* 1985; **64**: 888–896.
8. Yassen KA, Bellamy MC, Sadek SA, Webster NR. Tranexamic acid reduces blood loss during orthotopic liver transplantation. *Clinical Transplantation* 1993; **7**: 453–458.
9. Cheema SP, Webster NR, Dunn F, Bellamy MC. Mediators of fibrinolysis in orthotopic liver transplantation. *Clinical Transplantation* 1996 (in press).
10. Buckels JA, Tisone G, Gunson BK, McMaster P. Low hematocrit reduces hepatic artery thrombosis after liver transplantation. *Transplantation Proceedings* 1989; **21**: 2460–2461.
11. Tisone G, Gunson BK, Buckels JA, McMaster P. Raised hematocrit—a contributing factor to hepatic artery thrombosis following liver transplantation. *Transplantation* 1988; **46**: 162–163.
12. Ramos H, Todo S, Kang, Y Felekouras, Doyle HR, Starzl T. Liver transplantation without the use of blood products. *Archives of Surgery* 1994; **129**: 528–533.
13. *Jehovah's Witnesses and the Question of Blood.* Brooklyn, NY: Watchtower Bible and Tract Society, 1977; 1–64.
14. Bontempo FA, Lewis JH, Van Thiel DH. The relation of preoperative coagulation findings to diagnosis, blood usage and survival in adult liver transplantation. *Transplantation* 1985; **39**: 532–536.
15. Erslev AJ. Erythropoietin. *New England Journal of Medicine* 1991; **324**: 1339–1345.
16. Goodnough LT. Clinical application of recombinant erythropoietin in the perioperative period. *Hematology/Oncology Clinics of North America* 1994; **8**: 1011–1020.
17. Koestner JA, Loren D, Nelson D, Morris J, Safcsak K. Use of recombinant human erythropoietin (r-HuEPO) in a Jehovah's Witness refusing transfusion of blood products. *Journal of Trauma* 1990; **30**: 1406–1408.
18. Akingbola OA, Custer JR, Bunchman TE, Sedman AB. Management of severe anemia without transfusion in a pediatric Jehovah's Witness patient. *Critical Care Medicine* 1994; **22**: 524–528.
19. Gaudiani VA, Mason HDW. Preoperative erythropoietin in Jehovah's Witnesses who require cardiac procedures. *Annals of Thoracic Surgery* 1991; **51**: 823–824.
20. Chernow B. Blood conservation in critical care—the evidence accumulates. *Critical Care Medicine* 1993; **21**: 481–482.
21. Shaw BW, Gordon RD, Iwatsuki S, Starzl TE. Retransplantation of the liver. *Seminars in Liver Disease* 1985; **5**: 394–401.

British Journal of Anaesthesia 1996; **76**: 744–746

EQUIPMENT

Validation of the Edslab dual lumen oximetry catheter for continuous monitoring of jugular bulb oxygen saturation after severe head injury

M. J. SOUTER AND P. J. D. ANDREWS

Summary

Continuous jugular bulb venous oximetry has been validated previously for periods of up to 12 h after calibration. We assessed a new Edslab venous oximetry catheter in 15 patients with brain injury in the intensive care unit. After insertion into the jugular bulb, the catheter was calibrated using a laboratory co-oximeter. Subsequent comparisons were made at varying intervals (range 20 min to 100 h); 78 paired samples were obtained during periods of stable recordings. Estimation of haemoglobin saturation by the methods correlated well ($r^2 = 0.97$, $P < 0.0001$). Mean difference(d) was small (0.28% (SD 2.35%)) and limits of agreement ($d \pm (\text{SD} \times 1.96)$) were acceptable (−4.88% to 4.32%). There was no appreciable drift and there was negligible bias. This catheter did not suffer from problems of light intensity described with other systems, and it provided acceptable accuracy for clinical use for periods of up to and exceeding 24 h after calibration. (*Br. J. Anaesth.* 1996; **76**: 744–746)

Key words

Brain, injury. Brain, ischaemia. Measurement techniques, oximetry. Monitoring, oxygen saturation. Oxygen saturation. Equipment, catheters oximetry.

Continuous jugular bulb venous oximetry has developed into a valuable monitoring tool in the care of patients after head trauma. A cannulation technique and assessment of equipment accuracy have been described [1]. A limiting factor was that the apparatus was valid for periods of up to 12 h after *in vivo* calibration. This apparatus used a 40-cm flexible reflectance spectrophotometric catheter which had been designed for use within the umbilical artery in neonatal intensive care. The Edslab 4-French gauge catheter (Baxter Healthcare Corporation, Irvine, CA, USA), designed for venous oximetry, has been introduced recently.

This catheter offers several design advantages in that it has improved distance measurement markings and uses a firmer material which reduces flexing and kinking, but permits insertion without perforation of vessel walls. It is coated with an antimicrobial heparin coating and is also reportedly less subject to drift than catheters described previously.

We performed a prospective study in patients with severe head injury in the intensive care unit comparing *in vivo* measurements with samples aspirated from the jugular bulb measured *in vitro* with a Corning 270 laboratory co-oximeter (Ciba-Corning Diagnostics Ltd, Halstead, Essex, UK).

Methods

We evaluated the catheter in 15 patients with brain injury. Ethics Committee approval was obtained in advance for insertion and validation of jugular bulb catheters, without informed consent, in this group of patients.

Patients were referred to the Regional Neurosurgical Unit at the Western General Hospital, Edinburgh, from Edinburgh and Southeast Scotland. Eleven patients had suffered traumatic head injury and four had suffered a subarachnoid haemorrhage of World Federation of Neurological Surgeons grade 4 or 5. All subjects scored less than 8 on the Glasgow coma score on their last neurological examination, before muscle paralysis and artificial ventilation of their lungs for CT scan, any requisite surgery and insertion of an intraparenchymal intracranial pressure monitor. They were then transferred to the intensive therapy unit where they were sedated, paralysed and their lungs ventilated to mild hypocapnia (Pa_{CO_2} 3.5–4 kPa).

All treatment and care followed standard procedures agreed within our unit. Catheters were inserted using the Seldinger technique in a manner similar to cannulation techniques described previously. A compression test was performed to identify the dominant internal jugular vein and then the vein was entered percutaneously, lateral to the carotid artery at the level of the cricoid cartilage, directing the needle towards the external auditory meatus [1].

An important difference was that, rather than using a Vygon 14-gauge Leadercath cannula as an introducer (which is not haemostatic and must be withdrawn subsequently), the catheter was inserted using an 18-gauge Cook needle and a Daig 7-gauge Fast-Cath introducer, which has a Buorst–Tuohy

---

M. J. SOUTER, MB, CHB, FRCA (Department of Clinical Neurosciences); P. J. D. ANDREWS, MD, FRCA (Department of Anaesthesia); Western General Hospital, Crewe Road South, Edinburgh EH4 2XU. Accepted for publication: December 21, 1995.

haemostatic valve. The fibreoptic catheter was covered by a Baxter catheter contamination shield. The introducer is sutured to skin, remaining within the vein and, with the sheath, allows manipulation of the catheter after insertion to maintain accuracy, in a manner similar to that of pulmonary catheter insertion. This arrangement has not been reported previously for insertion into the internal jugular vein.

Catheters were inserted 15–20 cm, depending on patient size. Satisfactory catheter tip position was checked radiologically, ensuring that the tip was above the lower border of the first cervical vertebrae and was not kinking. This reduces extracranial contamination from the facial vein and reflectance errors. The catheter was connected to a Baxter Edwards Explorer System (Baxter Healthcare Corporation, Irvine, CA, USA) which contains an optical module and signal processor. The reading obtained was then calibrated against jugular venous samples analysed by a Corning 270 co-oximeter.

Subsequent comparisons were made at various intervals (mode 195 min; range 20 min to 100 h). If differences between catheter and co-oximeter values exceeded 5 %, the catheter was recalibrated. Samples were obtained slowly during periods of stable recordings (< 3 % oscillation).

Co-oximeter and catheter measurements were compared using linear regression and the method comparison technique recommended by Altman and Bland [2].

Results

Paired recordings ($n = 78$) were compared between 15 catheters and the co-oximeter using the difference in jugular saturation, the average difference and the SD of this difference to assess agreement between methods of measurement. These were also compared against time since the previous calibration, illustrating drift (fig. 1).

Forty-four samples were obtained at intervals of up to 24 h and 34 samples at intervals of 24–100 h. There was no appreciable drift, with accuracy being maintained, in some cases, to 3 or 4 days without recalibration.

There were only two points at which catheters required recalibration because they exceeded the 5 % agreement limits (errors of 7 % and 6 %, respectively). Estimation of haemoglobin saturation by the two methods correlated well ($r^2 = 0.97$, $P < 0.0001$) (fig. 2). Mean difference was small (−0.28 % (SD 2.35 %)) and limits of agreement (mean − (SD × 1.96)) were acceptable clinically (−4.88 % to 4.32 %).

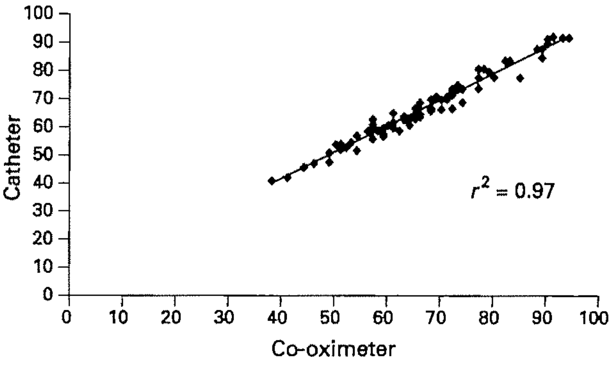


Figure 2 Co-oximeter *vs* catheter haemoglobin saturation readings.

Individual catheter mean differences were all within the limits of agreement (fig. 3). There was negligible bias on a method comparison plot (fig. 4), with 95 % confidence intervals of bias ($d \pm (t \times \text{SEM})$) of 0.25 % to −0.81 %.

Mean change in haemoglobin concentration over the period of monitoring was 0.68 (range 0–4.8) g dl^{-1}. There was no relationship between changes in haemoglobin concentration and catheter/co-oximeter measurement differences.

Discussion

Continuous jugular venous oximetry has been criticized previously because of the high degree of drift and requirement for frequent recalibration [3]. We have noted significant errors even with 12-hourly calibration. This problem was aggravated by inability to rectify position after misplacement or slippage. The advantage of the previous Oximetrix 3 system was that it was a triple wavelength system providing two light intensity ratios with a theoretically superior accuracy. A large number of the readings are discarded however because of light intensity alarms and drift errors, which is not surprising, given the limited venous flow present.

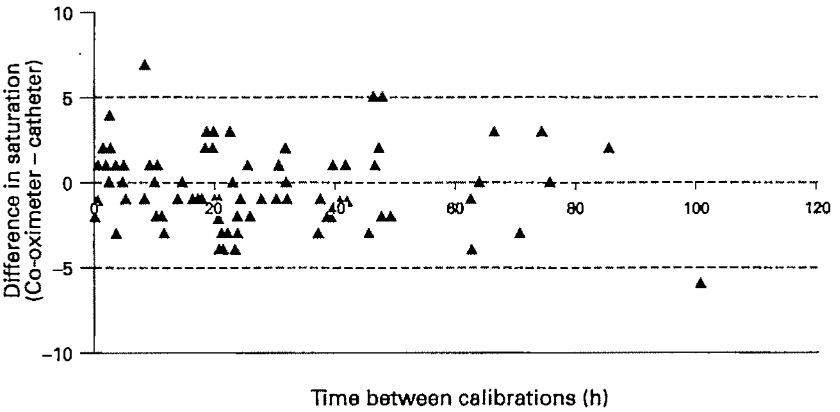


Figure 1 Difference in haemoglobin saturation between the co-oximeter and catheter with time.

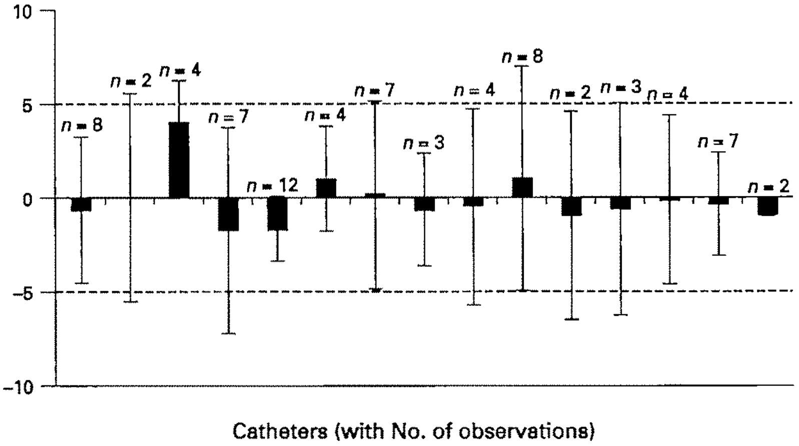


Figure 3 Mean difference (2 SD) in saturation between the co-oximeter and individual catheters.

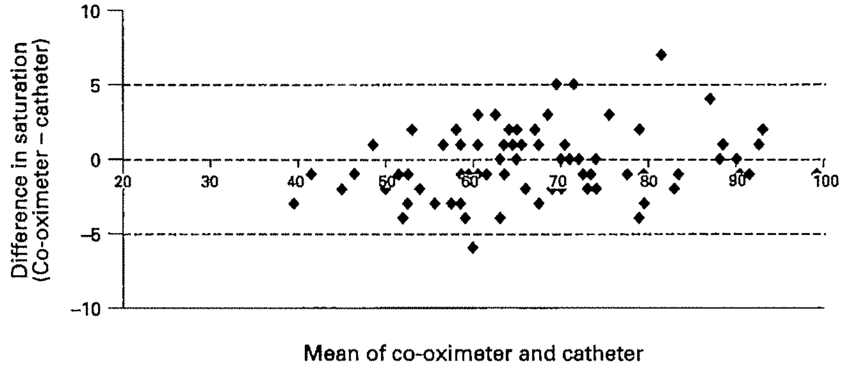


Figure 4 Method comparison plot of difference in haemoglobin saturation between the co-oximeter and catheter.

The Edslab catheter is a dual wavelength system which relies on haemoglobin concentration or packed cell volume being entered during calibration. These values are unlikely to change dramatically from day to day in this patient population and the system appears to be tolerant of minor fluctuations with the benefit of a greatly reduced degree of drift and relative independence of light intensity in a poor flow environment.

The Edslab catheter provides acceptable degrees of accuracy for clinical use for periods up to and exceeding 24 h after *in vivo* calibration. We are unable to give a threshold of time over which readings are invalid or suspect. Theoretically, significant changes in packed cell volume may introduce error into the system and should probably necessitate recalibration; this process requires the current laboratory measured haemoglobin concentration or packed cell volume. The mean change in haemoglobin concentration per patient was small (0.68 g dl^{-1}). However, we have observed changes of up to 4 gl dl^{-1} in haemoglobin concentration between measurements without loss in accuracy. It is also true that this patient population, when resuscitated, usually maintain a stable packed cell volume.

Nevertheless, we would suggest that daily recalibration is an easy compromise and within the bounds of maintained accuracy. For two catheters there were only two comparisons made after the initial calibration. However, in both cases the time interval was greater than 24 h and on that basis the comparisons made indicated a satisfactory performance over time.

The identification of a suitable introducer allows manipulation of catheter position and maintenance of accurate readings. In conjunction they represent a significant improvement in the quality of clinical monitoring.

References

1. Andrews PJD, Dearden NM, Miller JD. Jugular bulb cannulation: description of a cannulation technique and validation of a new continuous monitor. *British Journal of Anaesthesia* 1991; **67**: 553–558.
2. Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies. *Statistician* 1983; **32**: 307–317.
3. Sheinberg M, Kanter MJ, Robertson CS, Contant CF, Narayan RK, Grossman RG. Continuous monitoring of jugular venous oxygen saturation in head-injured patients. *Journal of Neurosurgery* 1992; **76**: 212–217.

British Journal of Anaesthesia 1996; **76**: 747–750

CORRESPONDENCE

Ventilatory response to carbon dioxide

Sir,—Saito and colleagues examined the influences of administration of morphine and lignocaine in the extradural space on the ventilatory response to carbon dioxide in female patients [1]. One of their observations was that ventilatory carbon dioxide sensitivity decreased significantly after morphine.

Saito and co-workers used a modification of Read's rebreathing method to obtain the ventilatory response to carbon dioxide [2]. Read introduced his method in 1967 which consists of rebreathing from a small rebreathing bag (4–6 litre) filled with 7% carbon dioxide in oxygen. The modification by Saito and colleagues was the use of a 10-litre rebreathing bag. Features that are observed when rebreathing is carried out in this way are [3–5]: end-tidal $P\text{CO}_2$ ($P\text{E}'_{\text{CO}_2}$) increases in a step-wise manner and rebreathing is initiated at a $P\text{CO}_2$ value close to that of mixed venous blood; rapid equilibrium is established between the $P\text{CO}_2$ of end-tidal, mixed venous and arterial blood, the gas in the rebreathing bag, and presumably also brain tissue $P\text{CO}_2$, all increase with the same rate of increase; ventilation ($\dot{V}\text{E}$) increases linearly in time and the $\dot{V}\text{E}$–$P\text{E}'_{\text{CO}_2}$ relation is linear; the rate of increase in $P\text{E}'_{\text{CO}_2}$ is independent of the ventilatory response; Read observed in an initial study in three subjects that the slopes of the $\dot{V}\text{E}$–$P\text{E}'_{\text{CO}_2}$ responses obtained from rebreathing and a steady-state method were not different.

Read's method allows acquisition of carbon dioxide sensitivity with minimal discomfort to the subject within a short period of time. Despite its popularity, there are several misconceptions regarding Read's rebreathing technique, especially when considering the effects of drugs on ventilatory control. Several recent studies have shown that carbon dioxide sensitivity from rebreathing exceeds steady-state carbon dioxide sensitivity by a factor of 2 [6–8]. The larger carbon dioxide sensitivity obtained from Read's method is explained by the increase in brain blood flow on increasing arterial $P\text{CO}_2$, resulting in a decreased cerebral venous to arterial gradient at steady-state (see [6]). Abolishing the mixed venous–arterial $P\text{CO}_2$ gradient to zero is insufficient to reduce brain tissue–arterial $P\text{CO}_2$ sufficiently close to zero. The mixed venous to arterial $P\text{CO}_2$ gradient is approximately 0.8 kPa in humans, while the jugular venous to arterial $P\text{CO}_2$ gradient is 1.5–2.0 kPa [9]. In contrast with the steady-state method, the measured carbon dioxide sensitivity from Read's rebreathing method depends on the magnitude of the initial step increase in $P\text{E}'_{\text{CO}_2}$ at the start of rebreathing and, to a lesser extent, on the subsequent rate of increase in $P\text{E}'_{\text{CO}_2}$ in time [9]. The larger the initial step increase in $P\text{E}'_{\text{CO}_2}$, the larger the measured carbon dioxide sensitivity. This is important when considering the effects of drugs that affect ventilatory control such as morphine. Ventilatory depression and the subsequent increase in $P\text{E}'_{\text{CO}_2}$ changes (i.e. decreases) the magnitude of the initial step increase in $P\text{E}'_{\text{CO}_2}$ at the start of rebreathing and consequently decreases the slope of the $\dot{V}\text{E}$–$P\text{E}'_{\text{CO}_2}$ response curve. This decrease may then reflect the change in initial conditions and not a drug effect on chemoreceptors, respiratory integration centres or the link between brainstem and respiratory movements.

However, an effect at these sites cannot be excluded. Read's rebreathing method yields results that are difficult and sometimes impossible to interpret. Bourke and Warley [8] showed this elegantly in a study comparing the steady-state method and Read's rebreathing method during i.v. administration of morphine. Morphine caused a decrease in the rebreathing carbon dioxide response slope, while the steady-state carbon dioxide response slope was shifted to higher $P\text{E}'_{\text{CO}_2}$ levels without any change in slope. They concluded that this parallel shift is specific to drugs acting on opioid receptors. Changes in overall and brain metabolism, steady-state brain blood flow and brain blood flow reactivity to carbon dioxide affect the rebreathing carbon dioxide response slope differently from the steady-state carbon dioxide response slope [9]. For example, drugs that reduce brain metabolism and steady-state brain blood flow cause a reduction in the rebreathing carbon dioxide response compared with the steady-state carbon dioxide response slope [9].

It is possible that the decrease in the $\dot{V}\text{E}$–$P\text{E}'_{\text{CO}_2}$ response slope after extradural morphine in the study of Saito and co-workers [1] is related to the above mentioned items.

In summary, we plead for the use of the steady-state method instead of Read's rebreathing method to study the effects of drugs on ventilatory control.

A. Dahan
A. Berkenbosch
Departments of Anesthesiology and Physiology
Leiden University Hospital
Leiden, The Netherlands

1. Saito Y, Sakura S, Kaneko M, Kosaka Y. Interaction of extradural morphine and lignocaine on ventilatory response. *British Journal of Anaesthesia* 1995; **75**: 394–398.
2. Read DJC. A clinical method for assessing the ventilatory response to carbon dioxide. *Australasian Annals of Medicine* 1967; **16**: 20–32.
3. Read DJC, Leigh J. Blood–brain tissue PCO$_2$ relationships and ventilation during rebreathing. *Journal of Applied Physiology* 1967; **23**: 53–70.
4. Rebuck AS, Slutsky AS. Measurement of ventilatory response to hypercapnia and hypoxia. In: Hornbein TF, ed. *Regulation of Breathing, Part II*. New York: Marcel Dekker Inc., 1981; 745–772.
5. Rebuck AS, Campbell EJM. A clinical method for assessing the ventilatory response to hypoxia. *American Review of Respiratory Disease* 1974; **109**: 345–350.
6. Berkenbosch A, Bovill JG, Dahan A, DeGoede J, Olievier ICW. Ventilatory CO$_2$ sensitivities from Read's rebreathing method and the steady-state method are not equal. *Journal of Physiology* (*London*) 1989; **411**: 367–377.
7. Jacobi MS, Patil CP, Saunders KB. Transient, steady-state and rebreathing responses to carbon dioxide in man, at rest and during light exercise. *Journal of Physiology* (*London*) 1989; **411**: 85–96.
8. Bourke DL, Warley A. The steady-state and rebreathing methods compared during morphine administration in humans. *Journal of Physiology* (*London*) 1989; **419**: 509–517.
9. Dahan A, Berkenbosch A, DeGoede J, Olievier ICW, Bovill JG. On a pseudo-rebreathing technique to assess the ventilatory response to carbon dioxide in man. *Journal of Physiology* (*London*) 1990; **423**: 615–629.

Sir,—We recognize the expertise of Drs Dahan and Berkenbosch in the field of ventilatory control and thank them for their valuable comments. We agree that Read's rebreathing technique (RB) is associated with results that are affected by various factors other than the central chemoreceptors and that the steady-state (SS) technique is suited to examine the effects of drugs on ventilatory control. However, the SS method did not fit in with our study design. The aim of our study was to investigate if extradural administration of lignocaine increased the risk of ventilatory depression induced by extradural morphine, which had been well established [1]. In contrast with morphine, transient effects of extradural lignocaine require a more strict study design regarding its baseline and use of a method that can be performed easily. While a measurement with RB can be completed within 6 min, SS takes more than 20 min to perform. Indeed, most previous studies examining the effect of extradural lignocaine have measured the ventilatory response 20–30 min after administration of local anaesthetic using RB [2]. One might argue that we could have used SS if a continuous infusion had been taken. However, on ethical grounds we could not take a longer time before surgery.

In interpreting our results, we should consider that the parallel shift of the carbon dioxide response curve without the decrease in slope in the SS method is specific to drugs acting on opioid receptors [3]. However, we believe that we can compare the ventilatory effects of extradural morphine and the combination of morphine and lignocaine, and conclude that extradural co-administration of lignocaine does not increase the risk of respiratory depression associated with morphine because the two groups include the same modulatory factors, as pointed out by Drs Dahan and Berkenbosch.

It is undeniable that we should choose the best technique available to obtain reliable results that are not contaminated by other undesirable factors in a scientific study. However, it is as important to use a technique that is practicable in a study using real patients.

Y. SAITO
S. SAKURA
Y. KOSAKA
Department of Anesthesiology
Shimane Medical University
Izumo City, Japan

1. Doblar DD, Muldoon SM, Abbrecht PH, Baskoff J, Watson RL. Epidural morphine following epidural local anesthesia: effect of ventilatory and airway occlusion pressure responses to CO_2. *Anesthesiology* 1981; **55**: 423–428.
2. Labaille T, Clergue F, Samii K, Ecoffey C, Berdeaux A. Ventilatory response to CO_2 following intravenous and epidural lidocaine. *Anesthesiology* 1985; **63**: 179–183.
3. Bourke DL, Warley A. The steady-state and rebreathing methods compared during morphine administration in humans. *Journal of Physiology (London)* 1989; **419**: 509–517.

Improving preoxygenation

Sir,—McGowan and Skinner are to be congratulated on their attempts to reproduce in their study some of the factors which confound our efforts at optimal preoxygenation in clinical practice [1]. It is reasonable to suppose that a leak around the face mask leads to less efficient denitrogenation of the lungs, but it is pleasing to see it demonstrated. However, reading this article prompted several questions.

First, how did the authors determine the order of the six "preoxygenations" performed by each volunteer? Were they randomized and, if not, would this tend to introduce an element of bias in that the subject's breathing pattern might alter during the course of the sequence? Did the subjects receive any specific training or instruction on what to do when breathing from the face mask? In my experience, when a patient is requested to "breathe normally" this may result in something quite abnormal, and the instruction to "take slow, deep breaths" may be more helpful. In a study such as this it might have been preferable to standardize on a particular minute volume, or at least have some estimate of peak inspiratory flow.

Second, do the authors think that sampling the gas stream further from the mouth might have improved their study? It is possible to introduce the tip of the sampling line into the nasopharynx, similar to Ooi, Joshi and Soni [2]. This would then have made it unnecessary to clamp the subjects' noses, more closely resembling clinical practice.

Third, while I can understand the choice of the Mapleson A system, why was a 4-litre reservoir bag used? Were any comparisons made between this and the standard 2-litre bag before selecting the latter? This is not usual clinical practice but, if it produces better results, perhaps it should be.

Fourth, what, if anything, was different about the subjects who did not reach an end-tidal oxygen concentration of greater than 0.9?

It is clearly important to use any manoeuvre which improves the efficiency of preoxygenation; substituting their standard face mask for another design (for instance the Everseal) might have produced better results by fitting certain faces more closely, and the authors may like to examine this. Berthoud, Read and Norman (using a fresh gas flow of 8 litre min^{-1}) showed that the Bain system was less efficient [3] and although more modern machines can deliver much higher flows, I have seen many trainees believing they are preoxygenating the lungs of patients with 6–8 litre min^{-1} of oxygen via the Bain system. The face mask seal is clearly important, but other factors need to be addressed if we are to improve the application of this vital technique.

A. F. SMITH
Department of Anaesthesia
North Manchester General Hospital
Manchester

1. McGowan P, Skinner A. Preoxygenation—the importance of a good face mask seal. *British Journal of Anaesthesia* 1995; **75**: 777–778.
2. Ooi R, Joshi P, Soni N. A high flow semi-open system for preoxygenation: an evaluation. *British Journal of Anaesthesia* 1992; **68**: 39–42.
3. Berthoud M, Read DH, Norman J. Preoxygenation—how long? *Anaesthesia* 1983; **38**: 96–102.

Sir,—It is clearly correct to say "it is reasonable to suppose" that a leak impairs preoxygenation. Our aim was to quantify the leak, not to embark on a wide ranging investigation of preoxygenation. In the light of this, the variations from normal practice are less important and were introduced after a pilot study to improve reproducibility.

Either oral breathing and sampling or nasal breathing and sampling were needed for reproducibility and we opted for the former. Ooi, Joshi and Soni [1] suggest that the latter would work equally well. A nasal sampling tube would probably have been less acceptable to subjects.

The six episodes of preoxygenation performed with each volunteer were carried out in the same increasing order of inspired oxygen concentration; following this, two experiments were performed with sub-optimal face mask seals and 100% oxygen. It is unlikely that this sequence introduced any bias as at least 15 min breathing room air were allowed for the individual to return to the pre-experimental state. Subjects were asked to place the face mask against their faces to produce a good seal, they were not required to hold it thereafter. Each subject was told to "breathe normally" and it was suggested that they close their eyes in order to make themselves feel more relaxed. The suggestion of standardizing minute volume would certainly lead to abnormal breathing; each subject has an individual natural minute volume. Peak inspiratory flow measurements may give an indication of abnormal breathing patterns but they would need validation against controls which would similarly be influenced by the abnormal environmental factors surrounding experiments such as this. Similar ventilatory frequencies were observed for each subject during each of the six preoxygenations.

Thus, although our study did not wholly reflect current UK clinical practice, we believe that we have quantified the magnitude of leaks with a sub-optimal mask fit and shown that they are appreciable.

The other questions, such as use of the "Everseal" masks or larger reservoir bags, clearly merit investigation in the future, but are not central to our work.

P. MCGOWAN
Department of Anaesthesia
Royal London Hospital
London
A. SKINNER
Department of Anaesthesia
Whiston Hospital, Merseyside

1. Ooi R, Joshi P, Soni N. A high flow semi-open system for preoxygenation: an evaluation. *British Journal of Anaesthesia* 1992; **68**: 39–42.

Serotonin in pre-eclampsia

Sir,—We read with interest the review article by Mushambi, Halligan and Williamson on recent developments in the pathophysiology and management of pre-eclampsia [1]. However, there was no mention of the possible role of serotonin which we believe may be important.

We suggest that serotonin, released from platelet aggregates, stimulates 5-HT_2 receptors causing generalized vasospasm and subsequent endothelial damage. Platelets could be attracted by embolic trophoblastic fragments which have been found in increased amounts in the venous circulation of women with pregnancy-induced hypertension compared with non-hypertensive controls [2, 3]. This role of serotonin is supported by Filshie and colleagues [4] who demonstrated increased concentrations of the serotonin metabolite 5-hydroxyindole acetate (5-HIAA) in the urine of pre-eclamptic patients. In addition, ketanserin, a 5-HT_2 receptor blocker, has been used successfully in the treatment of pre-eclampsia [5, 6]. Clearly, the role of 5-HT_2 receptor blockers in the management of pre-eclampsia and eclampsia requires further study.

N. M. Gajraj
C. Hutter
Department of Anaesthesia
City Hospital
Nottingham

1. Mushambi MC, Halligan AW, Williamson K. Recent developments in the pathophysiology and management of pre-eclampsia. *British Journal of Anaesthesia* 1996; **76**: 133–148.
2. Jaammeri KEU, Koivuniemi AP, Caroen EO. Occurrence of trophoblasts in the blood of toxaemic patients. *Gynaecologia* 1965; **160**: 315–320.
3. Chua S, Wilkins T, Sargent I, Redman C. Trophoblast deportation in pre-eclamptic pregnancy. *British Journal of Obstetrics and Gynaecology* 1991; **98**: 973–979.
4. Filshie GM, Maynard P, Hutter C, Cooper JC, Robinson G, Rubin P. Urinary 5-hydroxyindole acetate concentration in pregnancy induced hypertension. *British Medical Journal* 1992; **304**: 1223.
5. Weiner CP, Socol ML, Vaisrub N. Control of pre-eclamptic hypertension by ketanserin, a new serotonin antagonist. *American Journal of Obstetrics and Gynecology* 1984; **149**: 496–500.
6. Hutter C, Crighton IM, Smith K, Liu DTY. The role of serotonin in pre-eclamptic hypertension. A review and case report. *International Journal of Obstetric Anesthesia* (in press).

Cost of volatile agents

Sir,—In 1992, Dion published a formula by which the cost of volatile agent use could be calculated [1]. I have recently had cause to use this for newer agents and UK prices. Colleagues may find it of use when dealing with their pharmacies, etc. The cost is calculated by:

$$\frac{PFTMC}{d2412}$$

where P = agent concentration (%), F = fresh gas flow (litre min^{-1}), T = time (min), M = molecular weight, C = price of the agent (£ ml^{-1}) and d = density of liquid agent (g ml^{-1}).

Using values taken from Dion, the British National Formulary [2] and the manufacturers, I have calculated that at a fresh gas flow of 1 litre min^{-1} for 1 h, the costs, in pounds sterling, at different concentrations are those shown in table 1.

Table 1 Costs of different volatile agents

	Concentration	
	1 %	1 MAC (adult in 100 % O_2)
Halothane	£0.172	£0.148
Enflurane	£0.428	£0.812
Isoflurane	£1.193	£1.431
Sevoflurane	£1.445	£3.189
Desflurane	£0.551	£3.306

Alternatively "gas induction" using 8 % sevoflurane at a fresh gas flow of 6 litre min^{-1} for 1 min costs £1.16p.

I. Barker
Department of Anaesthesia
Sheffield Children's Hospital NHS Trust
Sheffield

1. Dion P. The cost of anaesthetic vapours. *Canadian Journal of Anaesthesia* 1992; **39**: 633.
2. British National Formulary. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 1995; 511–512.

Effect of transdermal hyoscine on nausea and vomiting

Sir,—I read with interest the recent article by Honkavaara on the effect of transdermal hyoscine on nausea and vomiting during and after middle ear surgery under local anaesthesia [1].

It was interesting, although not surprising, that the incidence of intra- and postoperative nausea and vomiting was lower in the treatment group (receiving prophylactic transdermal hyoscine) than in the placebo group, who received no prophylactic antiemetic treatment, as the antiemetic properties of hyoscine are already well known and documented [2, 3].

Honkavaara makes the assumption that the reduction in nausea and vomiting in the hyoscine group, in relation to motion sickness, may result from specific inhibition of the postsynaptic potential in the neurones of the vestibular nuclei. This may well be so, but one fact appears to have been overlooked in the design of the study. The two groups received preoperative oxycodone and intraoperative fentanyl, both of which have emetic side effects. The placebo group therefore received potentially emetic drugs without prophylactic antiemetic treatment. This would influence the incidence of nausea and vomiting in its own right, and the assumption that the reduction in nausea and vomiting in the hyoscine group was caused by reduced stimulation of the vestibular apparatus cannot be validated. One can only speculate on how the results would have been affected if another group had been included, receiving prophylactic antiemetic therapy known not to be as effective as hyoscine in motion sickness, such as metoclopramide.

R. N. Foster
Department of Anaesthesia
Hope Hospital
Salford

1. Honkavaara P. Effect of transdermal hyoscine on nausea and vomiting during and after middle ear surgery under local anaesthesia. *British Journal of Anaesthesia* 1996; **76**: 49–51.
2. Semple P, Madej TH, Wheatley RG, Jackson IJ, Stevens J. Transdermal hyoscine with patient-controlled analgesia. *Anaesthesia* 1992; **47**: 399–401.
3. Bailey PL, Streisand JB, Pace NL, Bubbers SJ, East KA. Transdermal scopolamine reduces nausea and vomiting after outpatient laparoscopy. *Anesthesiology* 1990; **72**: 977–980.

Sir,—I agree with Dr Foster that one of the causes of multifactorial postoperative nausea and vomiting (PONV) after middle ear surgery might be the emetic effect of the opioids used. However, I would hesitate to ascribe significance to opioids in this type of surgery causing physical stimuli to the inner ear. The amount of opioids used (oxycodone or fentanyl) did not predict PONV in middle ear surgery, as assayed by logistic regression analysis [1, 2].

In patients undergoing middle ear surgery, the noise from the drilling and suctioning exceeds 107 dB(A) in the mastoid cavity and furthermore, low frequency vibrations caused by the slowly rotating cutting burr can lead to a Tullio-phenomenon-like state [2]. In the Tullio phenomenon, sound pressure induces electrical potentials equivalent to cochlear microphonics from different receptors of the vestibular labyrinth leading to vestibular stimulation [3]. Patients with chronic otitis media or cholesteatoma are more susceptible to the Tullio phenomenon than healthy controls [3].

Dr Foster suggests that another group receiving metoclopramide should be included in the design of the study. This seems to be unjustified on the following grounds. Even though several studies support the efficacy of metoclopramide in PONV, there is at least an equal number of reports which do not confirm this result. Rowbotham concluded in his review [4] that i.v. administration of metoclopramide at induction appeared to be ineffective against PONV.

Thus the results presented in this letter and in earlier reports [1, 2] suggest that physical stimuli resulting in vestibular dysfunction are the main cause of the emetic episodes associated with ear surgery. The contributing effect of opioids on PONV, possibly sensitizing the vestibular system, is unclear, but it should be of equal intensity in both the placebo and hyoscine groups because of the same amount of opioid received by both groups.

P. HONKAVAARA
Otolaryngological Hospital
University Central Hospital
Helsinki, Finland

1. Honkavaara P. Effect of transdermal hyoscine on nausea and vomiting during and after middle ear surgery under local anaesthesia. *British Journal of Anaesthesia* 1996; **76**: 49–53.
2. Honkavaara P. Effect of ondansetron on nausea and vomiting after middle ear surgery under general anaesthesia. *British Journal of Anaesthesia* 1996; **76**: 316–318.
3. Ishizaki H, Pyykkö I, Aalto H, Starck J. Tullio phenomenon and postural stability: Experimental study in normal subjects and patients with vertigo. *Annals of Otology, Rhinology and Laryngology* 1991; **100**: 976–983.
4. Rowbotham DJ. Current management of postoperative nausea and vomiting. *British Journal of Anaesthesia* 1992; **69** (Suppl. 1): 46S–59S.

Gastric tonometry

Sir,—In a recent letter [1], Dr Fiddian-Green stated that an article written by us [2] was deficient and misleading. In support of his allegations Dr Fiddian Green cited three letters [3–5]. None of these letters was written by him at the time, and none found our article either "deficient" or "misleading". Our article clearly states that the purpose was to "...investigate the association between pH_i and other measures of metabolic acidosis..." by examining correlations between measurements. The numbers of patients involved were too small to make statements concerning any predictive effect, and no such claims were made. All three letters erroneously implied that this was the purpose of our study. Also, the letters suggested that there might be some patients in whom measurement of "intramucosal" pH might provide additional information. We made the same point, stating that we are unable to "...exclude the possibility that there are some patients with selective splanchnic ischaemia not reflected by systemic acidosis...". This hardly represents deficiency or an attempt to mislead.

Dr Fiddian-Green [1] went on to describe two studies [6, 7] which showed results contradictory to ours. He stated that these studies were more definitive, but did not mention others which disagreed with aspects of their results. Maynard and colleagues [6] showed that intramucosal pH was a better predictor of outcome than base deficit. However, continued data collection from the same institution, recording the same variables, has not confirmed the original findings. A retrospective analysis of a clinical database of 214 patients admitted to intensive care [8] showed that by 12 h after admission, base deficit was significantly different between survivors and non-survivors. This difference was found only for intramucosal pH at 24 h. Furthermore, analysis of ROC curves showed that discrimination by intramucosal pH was no greater at any time than measurement of base deficit. The authors concluded that "the routine measurement of [intramucosal] pH_{im} in clinical practice does not contribute additional information about likely outcome over and above that available from the simultaneous measurement of base excess and arterial pH".

In the careful study of Gutierrez and colleagues [7], three data points were collected for 21 patients, while investigating the effect of dobutamine on intramucosal pH. They did not specifically study the correlation between the variables, but the data showed that an increase in the mean value of intramucosal pH after infusion of dobutamine was not accompanied by an increase in the mean value for base deficit. Interestingly, a more recent study [9] on the effects of dobutamine on intramucosal pH has shown contrasting results, although the results of blood-gas analysis were not given. In this study dobutamine reduced intramucosal pH, particularly in patients who already had low intramucosal pH and low cardiac output. While the two carefully conducted studies quoted by Dr Fiddian-Green [6, 7] clearly suggested results different from our own, it is unclear as to which of these studies is the more "definitive".

O. BOYD
R. M. GROUNDS
Department of Anaesthesia
St George's Hospital
London

1. Fiddian-Green RG. Gastric tonometry. *British Journal of Anaesthesia* 1995; **75**: 507–508.
2. Boyd O, Mackay CJ, Lamb G, Grounds RM, Bennett ED. Comparison of the information gained from routine blood gas analysis and from gastric tonometry for intramural pH. *Lancet* 1993; **341**: 142–146.
3. Maynard ND, Atkinson S, Pierre DR. Routine blood-gas analysis and gastric tonometry for intramural pH. *Lancet* 1993; **341**: 691–692.
4. Schlichting E, Lyberg T. Routine blood-gas analysis and gastric tonometry for intramural pH. *Lancet* 1993; **341**: 692.
5. Mythen MG, Salomn JB, Webb AR. Routine blood-gas analysis and gastric tonometry for intramural pH. *Lancet* 1993; **341**: 692–693.
6. Maynard N, Bihari D, Beale R, Smithies M, Baldock G, Mason R, McColl I. Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure. *Journal of the American Medical Association* 1993; **270**: 1203–1210.
7. Gutierrez G, Clarke C, Brown SD, Price K, Ortiz L, Nelson C. Effect of dobutamine on oxygen consumption and gastric mucosal pH in septic patients. *American Journal of Respiratory and Critical Care Medicine* 1994; **150**: 324–329.
8. Atkinson S, Maynard N, Pierre D, Mason R, Smithies M, Bihari D. Gastric intramucosal pH (pHi) and systemic acid–base balance. *Shock* 1994; **2**: S30.
9. Parviainen I, Ruokonen E, Takala J. Dobutamine-induced dissociation between changes in splanchnic blood flow and gastric intramucosal pH after cardiac surgery. *British Journal of Anaesthesia* 1995; **74**: 277–282.

Measurement of competence

Sir,—Ellis's editorial [1], using the stimulus of Kestin's application of cusum analysis in the assessment of training [2], had me nodding in agreement until the concluding paragraph: "A quantitative approach to *education* is overdue. In the past there has been too much reliance on examinations as the only guide to the acquisition of *knowledge*." (My italics.) Training is not education; skills are not knowledge [3]. McManus listed the differentiating characteristics. For a course intended to educate, competency is not easy to assess, nor is the content of the course readily definable in any core curriculum. Training can be taught by restrictive methods, without insight, and the content of the course is readily put into compartments and tested in parts.

Before we go further down the road of syllabuses and structured training, we should stop to ask if we are training or educating.

N. W. GOODMAN
University Department of Anaesthesia
Southmead Hospital
Bristol

1. Ellis FR. Measurement of competence. *British Journal of Anaesthesia* 1995; **75**: 673–674.
2. Kestin IG. A statistical approach to measuring the competence of anaesthetic trainees at practical procedures. *British Journal of Anaesthesia* 1995; **75**: 805–809.
3. McManus IC. Examining the educated and the trained. *Lancet* 1995; **345**: 1151–1153.

British Journal of Anaesthesia 1996; **76**: 751

BOOK REVIEWS

600 MCQs in Anaesthesia: Clinical Practice, 2nd Edn. N. W. GOODMAN AND C. JOHNSON. Published by Churchill Livingstone, London. Pp. 285; indexed. Price £12.50.

This is the second edition of an MCQ book first published in 1987 and is designed for those preparing for the final part of the FRCA. It covers the subjects of anaesthesia, medicine and surgery. Although many of the subjects overlap with the primary FRCA (that replaces the old part 1), the material is not appropriate for those preparing for that examination.

There is a useful section at the beginning of the book on technique, giving helpful advice on strategies for answering MCQs and on self-testing. The book consists of 20 mock papers with 30 stem questions of five parts each. The length of these "papers" is designed so that they can be completed in 45 min, which is an appropriate period to find for private study. The answers are well separated from the questions and include some explanation.

This book is a considerable improvement on the first edition that contained a number of questions that had become outdated. The new edition also contains fuller explanations to the answers, those in the earlier edition being rather limited. Although the book is designed for mock MCQ practice, there is an index of subjects that also allows for its use as a revision aid and to identify areas requiring further study.

This is a useful book for those preparing for the final FRCA (old part 3), both for practising MCQ technique and as a study aid. I would recommend it to them.

J. Raphael

Regional Anesthesia: An Atlas of Anatomy and Techniques. M. B. HAHN, P. M. MCQUILLAN AND G. J. SHEPLOCK (editors). Published by Mosby, St Louis, USA. Pp. 311; indexed; illustrated. Price £99.50.

The past decade has seen a veritable explosion in the number of books available to inform the practitioner of regional anaesthesia and any new product must offer something additional to the existing volumes. This book has achieved this because it is based on the work of the third editor, George Sheplock, who has combined traditional anatomical dissection with modern imaging techniques and computer-based display methods to build three-dimensional pictures. The application of these to regional anaesthesia is entirely appropriate because it is important that the practitioner thinks beyond the two-dimensional surface through which the needle is inserted and considers the structures that are encountered as the needle tip is advanced. This concept should apply as much to those structures that should *not* be encountered, as to those that should!

Two types of illustrations are used commonly. The first is a pair of pictures, one a traditional anatomical section and the other an exactly corresponding computer-enhanced and labelled image of the same section. The second illustrative method is to superimpose an anatomical dissection on a clinical photograph to the same scale to create an anatomical "window". The former method works well, but I am less impressed with the latter, perhaps because the size of the "window" tends to be rather small. However, a beginner might find them more useful. There are many other, more traditional type illustrations and many (clinical photographs and line diagrams) are of such a high standard that I wonder if concentrating on these more traditional methods would have been more successful. The gold standard in this area of publishing is Eriksson's *Handbook,* a work which is now nearly 30 years old, but for all its modern illustrative methods this book still fails to reach that standard of clarity of illustration.

In a work presented as an atlas, text is clearly of secondary importance, but in regional anaesthesia the "do's and don'ts", and answers to questions such as "how, why and when" are just as important as "where". Each chapter describing an individual block technique has a short section of text, all by acknowledged experts in the field of regional anaesthesia, but there is rarely sufficient information to provide all the necessary instruction and knowledge. There are two short introductory chapters, one on pharmacology and the other on general guidelines for practice. These add to the value of the volume, but are not comprehensive and the book would have been better produced as an atlas of anatomy for regional block rather than as an instructional manual. If it is approached as a source of helpful anatomical illustrations it works well. The quality of illustration and book production is high, but is reflected in the price. Many teachers of regional anaesthesia may find it useful to have a copy, but I doubt if it merits a place in the departmental library, particularly as some of the illustrations depicting needle insertion (e.g. stellate ganglion block) do not convey the correct approach and none depict appropriate aseptic technique. I appreciate the difficulties, but it is possible to produce informative pictures with drapes, etc., in place.

J. A. W. Wildsmith

Essentials of Anaesthetic Equipment. B. AL-SHAIKH AND S. STACEY. Published by Churchill Livingstone, Edinburgh. Pp. 147; illustrated. Price £20.00.

This is a beautifully designed and produced book of size 7½ × 9½ inches in triple column format. The text is lavishly illustrated with diagrams and colour photographs of high quality. Although many colour illustrations are small, they are perfectly clear, with the odd exception (e.g. fig. 10.18). The cost of the colour printing has been met by several medical companies, otherwise the price of production would have been prohibitive.

The text is easy to read and consists of short numbered paragraphs of short sentences. Topics covered include: medical gas supplies; the anaesthetic machine; scavenging of gases and vapours; breathing system; tracheal and tracheostomy tubes and airways; masks; laryngoscopes and tracheal intubation equipment; lung ventilators; humidification; monitoring; pain management and regional anaesthesia; and equipment used in intensive care. There are two appendices, both authorized by the Association of Anaesthetists of Great Britain and Ireland (AAGBI). The first is the elements of *Checklist for Anaesthetic Machines* published in 1990, and the second is their *Recommendations for Standards of Monitoring during Anaesthesia and Recovery* published in 1988. Presumably the revised 1994 version of the latter came too late for inclusion in this book. Nevertheless, only the very basic main points of the summary of "monitoring" are included in the appendix and not to have provided a more comprehensive account gives a poor impression of the input of the AAGBI into such an authoritative area of clinical practice.

A knowledge of anaesthetic equipment has always been the mainstay of the specialty. Obviously, the authors had to be selective in choosing what topics to include. However, it is amazing that so much has been included in a book of only 147 pages. Sadly, there is not one reference in the whole of the book so the reader is deprived of the chance to extend his reading or to appreciate the enormous work done by the inventors of anaesthetic equipment. The book is refreshingly up to date and should be a runaway best seller. It is thoroughly recommended not only to trainee anaesthetists but to others in the anaesthetic team. It is marvellous value for money.

A. P. Adams

Papers for publication and all editorial communications should be addressed to:
Professor G. Smith,
Editor, British Journal of Anaesthesia,
University Department of Anaesthesia,
Leicester Royal Infirmary,
Leicester LE1 5WW.
Telephone: 0116 247 0141
Fax: 0116 285 4487

All **business communications** should be sent to the Publishers: Professional & Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR.

For advertisement sales, contact Sheila Rowe (Tel. 0171 383 6330; Fax 0171 383 6556).

The GUIDE TO CONTRIBUTORS may be found in the advertisement section of any issue of the journal (pages ii, iv & vi).
Published monthly. Annual subscriptions: Worldwide £156.00; USA only $245.00 (direct orders only). Trainee rate: Worldwide £75.00. Airmail rates on application. ISSN 0007–0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London WC1H 9JR. Orders in the USA may be sent to Professional and Scientific Publications, PO Box 408, Franklin, MA 02038, USA.

"WIREX" self-binding cases, which hold a complete volume, i.e. 6 months with room for a supplement and annual handbook, are now available. Price UK £14.00 per two binders, Europe £20.00 per two binders (to cover 1 year). Price includes postage and packing. Rest of the World prices on application. Cheque with order to Hethersett Supplies, Mount Bovers Lane, Hawkwell, Essex SS5 4JA, Tel. (01702) 202393.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statements appear in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statements. Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

© Copyright: 1996 *British Journal of Anaesthesia*
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia*, requests for which should be addressed to the **Publishers**.

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge.

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 76, No. 6 JUNE 1996

EDITORIAL I

Impact factors in anaesthesia journals

For many years, there have been attempts to assess journals in terms of the quality or importance of the information they contain. Perhaps the best known is the Science Citation Index (SCI) developed in the 1960s in the United States by a commercial organization, the Institute for Scientific Information (ISI). This organization produces what is the most widely known measure and generally believed to be an index of a journal's scientific quality, namely the SCI impact factor. As noted in a previous editorial in this journal [1], impact factors have assumed increasing importance in Western Europe where in many countries they have been used as part of internal promotion procedures for academic staff, and in the UK they have been used to some extent recently in the research assessment exercise [1].

The impact factor is a measure of the frequency with which an average article in a journal has been cited in a particular year. For the SCI, it is calculated by dividing the number of all current citations of items published in Journal X in the previous 2 yr, by the number of articles published in Journal X during those 2 years. Another commonly used index is the cited half-life which describes the number of journal publication years going back from the current year which account for 50% of the total citations received by the cited journal in the current year.

Table 1 lists the impact factors and citation half-lives for the 12 anaesthesia journals with the highest ratings for the year 1994 and this refers to articles appearing in 1992–93. The impact factors for the year 1995 will not be available until the autumn of year 1996.

Despite the superficial attraction of the impact factor as an objective evaluation of the quality of the journal, there are considerable problems with this concept and these factors must be used cautiously; in particular, comparisons between different journals should be made with great care. In a brief evaluation of recent literature on impact factors, the majority of articles were hostile to the usefulness of impact factors as an index of the quality of a journal [2–6], with the exception of a recent letter in *Lancet* [7].

The problems inherent in the interpretation of impact factors have been reviewed extensively by Séglen from Oslo [4–6]. He described four major areas of concern which impeded the use of impact factors for evaluation of quality; namely citation bias, incomplete journal coverage, author variability and field effects.

It will be obvious to even the most inexperienced reader of scientific journals that there is considerable bias in the choice of articles for citation. Apart from the clear tendency of North American authors to cite the North American literature and for Europeans to demonstrate similar chauvinism, other factors include self-advertising (self-citation), flattery, within-institution parochialism, lack of knowledge of the literature and attempts to ingratiate the authors with the referees for a journal. Perhaps the largest citation bias is the failure of English speaking authors to cite articles in non-English scientific literature.

The SCI covers only a small proportion of the total scientific literature available. For the most part, this does not usually exclude the majority of anaesthetic literature but there is no attempt to assess the accuracy of data incorporated on the database of SCI.

The choice of a short period of time from which citations are made to a particular journal also introduces a confounding factor. Clearly, it would be more appropriate if some index were obtained of the lifetime citation of specific articles.

Séglen [5] has drawn attention to the fact that the greatest impediment to the use of impact factors in the evaluation of scientific work is the difference that clearly exists between different scientific fields. It will be clear from examining the list of impact factors for different journals that some disciplines seem to have higher impact factors than others. In rapidly developing fields such as immunology and molecular biology, journal impact factors tend to be much higher than in more established fields where the rate of change is not dramatic, for example in some of the clinical disciplines such as ophthalmology.

Table 1 Impact factors for 1994 available in late 1995; these relate to articles published in 1992–93

Journal	Impact factor	Citation half-life
1. *Anesthesiology*	4.711	6.2
2. *British Journal of Anaesthesia*	2.298	6.4
3. *Anesthesia and Analgesia*	2.166	5.8
4. *Anaesthesia*	1.813	5.6
5. *Canadian Journal of Anaesthesia*	1.433	5.3
6. *Journal of Neurosurgical Anaesthesia*	1.433	2.6
7. *Anaesthesia and Intensive Care*	0.996	4.8
8. *Acta Anaesthesiologica Scandinavica*	0.939	6.8
9. *Regional Anesthesia*	0.873	4.4
10. *European Journal of Anaesthesiology*	0.567	3.9
11. *Anaesthetist*	0.557	6.0
12. *Annals of French Anaesthesia*	0.194	5.1

In general terms, it is also obvious that basic science journals tend to have higher impact factors than clinical journals. The reason is clearly that clinical investigations may be dependent on basic science investigations for developing hypotheses or invoking mechanisms of clinical effects while the converse is less common. Consequently, there is a 3–5 fold difference in citations between clinical medicine and basic science medicine.

The geographical size of a scientific community also has a marked impact because of the tendency for citation of articles from friends or colleagues encountered frequently at scientific meetings. Thus in general terms, journals published in North America and catering largely for the North American market have higher impact factors than those published in Europe.

In a recent study, Séglen investigated the relationship between the extent to which a specific article was cited and journal impact factors by assessing complete publication lists provided by 16 senior scientists from a single institution in Norway [4]. He found a very skewed distribution in journal impact values and also in the distribution of article citedness leading to a poor general correlation between journal impact factor and article citedness. The major conclusion which he drew from this study was that the extent to which a particular article was cited in the literature was not influenced appreciably by the status of the journal in which it was published. Despite this, there seems to be a general assumption that authors send their work to journals with the highest impact factors. While it is true that highly cited articles tend to appear in high impact factor journals, Séglen concluded that it was not because the articles were published in a high impact factor journal that they were cited but that the converse existed, namely that some journals had high impact because they published high impact articles.

It has also been suggested recently that impact factors favour short-term studies [3]. Hansson plotted impact factors (IF) against pattern factor (PF), calculated as the number of citations of articles in a 2-yr period divided by the number of articles in the journal during the same 2-yr period; a high correlation was found between IF and PF [3]. He concluded that IF was predicted by the habit of citing articles published within 2 yr thus favouring areas that generate short-term studies. This conclusion was disputed by Brody on the grounds that two clinical journals with the highest impact factors had published many long-term studies [7]. Interestingly, in a survey of scientists at NIH who were asked to list the most prestigious journals in rank order, there was no correlation between these rankings and journal impact factors [2].

Despite the problems inherent in impact factors, the desire to quantify the "quality" of both articles and journals is unlikely to wane. However, for reasons many of which are outlined above, great caution should be exercised in the interpretation of these data. They may be useful to follow the fortunes of an individual journal but comparison between journals of difficult geographical origin or specialty is fraught with problems.

G. SMITH
Editor

References

1. Smith G. Research in anaesthesia—the key to the future. *British Journal of Anaesthesia* 1995; 75; 383–386.
2. Foster WR. Impact factor as the best operational measure of medical journals. *Lancet* 1995; **346**: 1301.
3. Hansson S. Impact factor as a misleading tool in evaluation of medical journals. *Lancet* 1995; **346**: 906.
4. Séglen PO. Causal relationship between article citedness and journal impact. *Journal of the American Society for Information Science* 1994; **45**: 1–11.
5. Séglen PO. The skewness of science. *Journal of the American Society for Information Science* 1992; **43**: 628–629.
6. Séglen PO. Citation frequency and journal impact: valid indicators of scientific quality? *Journal of Internal Medicine* 1991; **229**: 109–111.
7. Brody S. Impact factor as the best operational measure of medical journals. *Lancet* 1995; **346**: 1300–1301.

British Journal of Anaesthesia 1996; **76**: 755–756

EDITORIAL II

Airway management in cleft lip and palate surgery

Cleft lip and palate are the most common of the craniofacial anomalies, with an incidence of approximately 1 in 800 live births. Twenty-five percent of cases of cleft lip are bilateral, and 85 % of these are associated with cleft palate. In recent years there has been a move towards earlier surgical repair of both cleft lip and palate, with cleft lip repair being performed in the neonatal period in some centres.

The presence of other associated congenital anomalies, including cardiac and renal anomalies, should always be borne in mind, particularly in children with isolated cleft palate. Over 150 syndromes have been described in association with cleft lip/palate, but fortunately all are rare. Some, however, have considerable anaesthetic implications, and many involve potential airway problems. The most well-known of these are the Pierre Robin, Treacher Collins and Goldenhar syndromes. Other, such as the Klippel-Feil syndrome, may include abnormalities of the cervical spine.

Airway problems in children with cleft lip and palate were recognized by Magill more than 70 yr ago [1], and since then many methods of managing the child with the difficult airway have been described. Some, such as the use of firm pressure over the larynx to aid laryngoscopy with a bougie as a guide to tracheal intubation, are relatively simple to perform by any competent anaesthetist and are successful in most cases. Digitally assisted tracheal intubation is used rarely, but also requires no special equipment [2]. Other more sophisticated methods, such as those involving fibreoptic techniques, require special equipment, training and experience [3, 4]. The laryngeal mask has been recommended as a guide to fibreoptic intubation in children [5] and has been used successfully in Pierre Robin [6–8] Treacher Collin [9] and Goldenhar syndromes [10]. It has been used for cleft palate repair in a baby with Pierre Robin syndrome when intubation proved impossible [11]. Specially designed light wands and laryngoscopes are available for difficult intubation in children [12–14], but these are either expensive or not readily available in most anaesthetic departments. Retrograde techniques have been described in infancy [15], but their success rate is much lower than in older children or adults. Even when a guide wire or bougie is manipulated successfully into the trachea, it may prove impossible to pass a tracheal tube over it. Threading the guidewire through the Murphy eye of the tracheal tube instead of the end hole allows an extra length of tube to pass into the trachea before withdrawal of the guidewire and this technique was used successfully in a 5-month-old infant with Goldenhar syndrome [16].

Assessment of the degree of difficulty of intubation before operation is not always possible in these children, as methods of assessment used in adults which require patient co-operation are not easy to apply in young infants. Radiological assessment of the paediatric airway has been described based on measurement of the maxillo-pharyngeal angle on lateral x-ray. This angle is normally greater than 100°, and angles less than 90° suggest that it will be impossible to see the larynx at laryngoscopy [17]. Awake fibreoptic intubation via a laryngeal mask has been described in an infant [10], but most anaesthetists perform laryngoscopic assessment of the airway during general anaesthesia. Anaesthesia is commonly induced with halothane, although sevoflurane may become the agent of choice in the future. Application of increased airway pressure with a well fitting face mask minimizes the risk of airway obstruction during induction. Neuromuscular blockers are contraindicated before intubation whenever the ability to inflate the lungs is in doubt. The applicability of adult gradings of the laryngoscopic view to children has not been evaluated widely, and the child with a difficult airway at induction will not necessarily have an airway that is difficult to intubate. Fibreoptic evaluation of the paediatric airway through an endoscopic face mask has been advocated recently [18], but is unnecessary in most cases.

In this issue, Gunawardana [19] reports the findings of a 10-yr prospective study of 800 consecutive patients presenting for cleft lip or palate surgery in whom an attempt was made to correlate the Cormack and Lehane gradings found at laryngoscopy [20] with the degree of difficulty experienced at intubation. All children were ASA I, and none was apparently suffering from any of the syndromes associated with cleft lip or palate. In 59 cases, however, the cleft lip was bilateral, and 52 children demonstrated retrognathia. Cormack and Lehane grading of III or IV, assessed after application of external laryngeal pressure, was associated with difficult intubation in 86 % of cases, and a lower grading in only 2 %. The degree of laryngoscopic difficulty decreased with increasing age, with no difficult laryngoscopies occurring in children aged 5 yr or more. This contrasts strikingly with conditions such as Goldenhar syndrome, where intubation often becomes more difficult with increasing age. Virtually all difficult laryngoscopies occurred in children with bilateral clefts or retrognathia. This finding is particularly encouraging, as both of these situations are readily assessed at the preoperative visit. The importance of carefully studying the child's profile at this time cannot therefore be emphasized too strongly. In infants with severe upper airway problems there is also usually a history of significant feeding difficulties.

Despite the laryngoscopic findings, failure to intubate occurred in only 1 % of patients in Gunawardana's series, all of whom were less than 6 months of age. There were no significant episodes of hypoxaemia. Heart rate decreased to less than 80 beat min^{-1} in nine children, but the clinical significance of this is impossible to assess without knowing their ages and resting heart rates. The author attributed these results largely to the use of a spontaneously breathing technique. However, intubation might have been successful in more infants had a straight-bladed laryngoscope been available or if neuromuscular blockers had been used to facilitate intubation when the ability to inflate the lungs manually had been confirmed. The use of neuromuscular blockers might also have reduced the incidence of airway bleeding. In a recent study, fewer children coughed during intubation using suxamethonium than alfentanil [21].

The presence of retrognathia or other congenital anomaly involving the upper airway may cause respiratory problems in the immediate postoperative period and extubation should be delayed until the child is awake. Provision of adequate postoperative analgesia is made more difficult because of the potential for respiratory depression which most analgesic drugs possess. Infraorbital nerve block offers an attractive alternative method of pain relief after cleft lip repair [22, 23].

D. J. HATCH
Portex Department of Anaesthesia
Institute of Child Health
30 Guilford Street
London WC1N 1EH

References

1. Hatch DJ. Magill's endotracheal catheter device for use during repair of cleft lip and palate. *Paediatric Anaesthesia* 1995; 5: 199–201.
2. Sutera PT, Gordon GJ. Digitally assisted tracheal intubation in a neonate with Pierre Robin syndrome. *Anesthesiology* 1993; 78: 983–985.
3. Hasan MA, Black AE. A new technique for fibreoptic intubation in children. *Anaesthesia* 1994; 49: 1031–1033.
4. Wrigley S, Black AE, Sidhu V. A fibreoptic laryngoscope for paediatric anaesthesia. *Anaesthesia* 1995; 50: 709–712.
5. Dubreuil M, Ecoffey C. Layngeal mask guided tracheal intubation in paediatric anaesthesia. *Paediatric Anaesthesia* 1992; 2: 344.
6. Baraka A. Layngeal mask airway for resuscitation of a newborn with Pierre-Robin syndrome. *Anesthesiology* 1995; 83: 645–646.
7. Chadd GD, Crane DL, Phillips RM, Tunell WP. Extubation and reintubation guided by the laryngeal mask airway in a child with the Pierre-Robin syndrome. *Anesthesiology* 1992; 76: 640–641.
8. Markakis DA, Sayson SC, Schreiner MS. Insertion of the laryngeal mask airway in awake infants with the Robin sequence. *Anesthesia and Analgesia* 1992; 75: 822–824.
9. Inada T, Fujise K, Tachibana K, Shingu K. Orotracheal intubation through the laryngeal mask airway in paediatric patients with Treacher-Collins syndrome. *Paediatric Anaesthesia* 1995; 5: 129–132.
10. Johnson CM, Sims C. Awake fibreoptic intubation via a laryngeal mask in an infant with Goldenhar's syndrome. *Anaesthesia and Intensive Care* 1994; 22: 194–197.
11. Beveridge ME. Laryngeal mask anaesthesia for repair of cleft palate. *Anaesthesia* 1989; 44: 656–657.
12. Krucylak CP, Schreiner MS. Orotracheal intubation of an infant with hemifacial microsomia using a modified lighted stylet. *Anesthesiology* 1992; 77: 826–827.
13. Cooper MG, Donnelly J, Overton JH. Assessment of an angulated laryngoscope for difficult paediatric intubation. *Paediatric Anaesthesia* 1993; 3: 33–36.
14. Baraka A, Muallem M. Bullard laryngoscopy for tracheal intubation in a neonate with Pierre-Robin syndrome. *Paediatric Anaesthesia* 1994; 4: 111–113.
15. Schwartz D, Singh J. Retrograde wire-guided direct laryngoscopy in a 1-month old infant. *Anesthesiology* 1992; 77: 607–608.
16. Cooper CMS, Murray-Wilson A. Retrograde intubation: management of a 4.8 kg, 5 month infant. *Anaesthesia* 1987; 42: 1197–1200.
17. Delegue L, Rosenberg-Reiner S, Ghnassia MD. L'intubation tracheale chez les enfants atteints de dysmorphie craniofaciales congenitales. *Anesthesia, Analgesia et Reanimation* 1980; 37: 133–138.
18. Frei FJ, àWengen DF, Rutishauser M, Ummenhofer W. The airway endoscopy mask: useful device for fibreoptic evaluation and intubation of the paediatric airway *Paediatric Anaesthesia* 1995; 5: 319–324.
19. Gunawardana RH. Difficult larynogoscopy in cleft lip and palate surgery. *British Journal of Anaesthesia* 1996; 76: 757–759.
20. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; 39: 1105–1111.
21. Steyn MP, Quinn AM, Gillespie JA, Miller DC, Best CJ, Morton NS. Tracheal intubation without neuromuscular block in children. *British Journal of Anaesthesia* 1994; 72: 403–406.
22. Ahuja S, Datta A, Krishna A, Reader MCH, Bhattacharya A. Infra-orbital nerve block for relief of postoperative pain following cleft lip surgery in infants. *Anaesthesia* 1994; 49: 441–444.
23. Bosenberg AT, Kimble FW. Infraorbital nerve block in neonates for cleft lip repair: anatomical study and clinical application. *British Journal of Anaesthesia* 1995; 74: 506–508.

British Journal of Anaesthesia 1996; **76**: 757–759

CLINICAL INVESTIGATIONS

Difficult laryngoscopy in cleft lip and palate surgery

R. H. GUNAWARDANA

Summary

We studied prospectively 800 paediatric patients undergoing repair of cleft lip and palate to determine the predictors of difficult laryngoscopy. The incidence of difficult laryngoscopy (Cormack and Lehane grade III and IV) was 2.95% in patients with unilateral cleft lip, 45.76% in bilateral cleft lip and 34.61% in patients with retrognathia. Tracheal intubation was successful in 99% of patients in whom laryngoscopy was difficult. There was a significant association between age and laryngoscopic view ($P < 0.01$). (*Br. J. Anaesth.* 1996; **76**: 757–759)

Key words

Anaesthetic techniques, laryngoscopy. Larynx, laryngoscopy. Surgery, plastic. Anaesthesia, paediatric.

Successful management of cleft and palate requires early surgery. It is imperative that the trachea of these patients be intubated, not only to maintain the airway, but to prevent aspiration. However, intubation may be difficult in the paediatric patient because of normal variations in airway anatomy. The difficulty may be exaggerated by the congenital anatomical anomaly.

Difficulties with intubation continue to be a major cause of anaesthesia-related morbidity, mortality and litigation [1, 2]. Preoperative identification of patients in whom intubation may be difficult may save lives. The existing bedside tests as predictors of difficult intubation [3–5] are not practical in children. Also, they are not sensitive or specific enough for routine use [6, 7]. The aim of this study was to determine the predictors of difficult laryngoscopy in paediatric patients presenting for repair of cleft lip and palate.

Patients and methods

During a 10-yr period (1985–1994), we studied prospectively 800 consecutive ASA I patients, presenting for cleft lip (533) and cleft palate (267) surgery. Patients were aged 2 months to 8 yr (65% were less than 1 year of age) and 49% were males.

Anaesthesia was induced with halothane and nitrous oxide in oxygen. Neuromuscular blockers were not administered. A towel roll was placed under the shoulders and laryngoscopy was performed with a small curved blade (Macintosh) laryngoscope when there was adequate jaw relaxation. The larynx was seen with the aid of external laryngeal compression. The distal end of the Portex tracheal tube was curved appropriately using a flexible introducer to aid in intubation.

The appearance at direct laryngoscopy after application of laryngeal pressure was recorded by the anaesthetist using the classification of Cormack and Lehane [8]. The relationship between congenital anomaly and laryngoscopic view and the association between age and view on laryngoscopy were studied. Data were analysed using the chi-square test.

Outcome of tracheal intubation was classified as easy (successful with one or two attempts), difficult (two to four attempts) and failed, when intubation was not possible with four attempts.

The lowest arterial oxygen saturation (Sp_{O_2}) and heart rate recorded during laryngoscopy were compared with values before laryngoscopy.

Results

The cleft lip was unilateral in 474 patients (172 involved the right or left lip with or without involvement of the alveolus, and in 302 the clefts involved the lip, alveolus and palate). In the 59 patients with bilateral cleft lip, the cleft passed down both sides of the premaxilla into the palate. Of the 267 patients with isolated cleft palate, 52 had retrognathia.

Laryngoscopy was easy (grade I or II) in 741 (92.62%) and difficult (grade III or IV) in 59 (7.38%) patients (fig. 1). There was a highly significant association between anomaly and laryngoscopic view ($P < 0.01$). The incidence of difficult laryngoscopy in each anomaly is shown in figure 2. In the bilateral clefts of the lip and alveolus, the protruding premaxilla obstructed the laryngeal view.

Of the 59 patients with difficult laryngoscopy, 39 (66.10%) were less than 6 months of age, 12 (20.34%) were 6–12 months and 8 (13.56%) were 1–5 yr old (table 1). There was a significant association between age and laryngoscopic view ($P < 0.01$). Laryngoscopy was easier with increasing age. The incidence of difficult laryngoscopy was 11.14% in children less than 6 months of age, 7.05% in the age group 6–12 months and 4.12% in 1–5 yr olds

---

R. H. GUNAWARDANA, DA, FRCA, Department of Anaesthesiology, Faculty of Medicine, University of Peradeniya, Sri Lanka.
Accepted for publication: January 8, 1996.

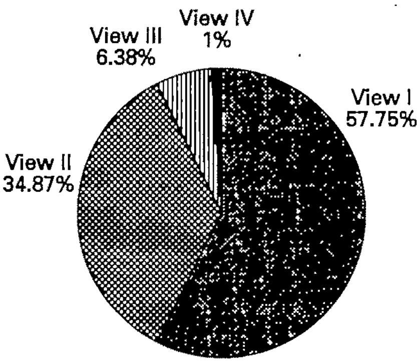


Figure 1 Percentage of patients in relation to laryngoscopic view.

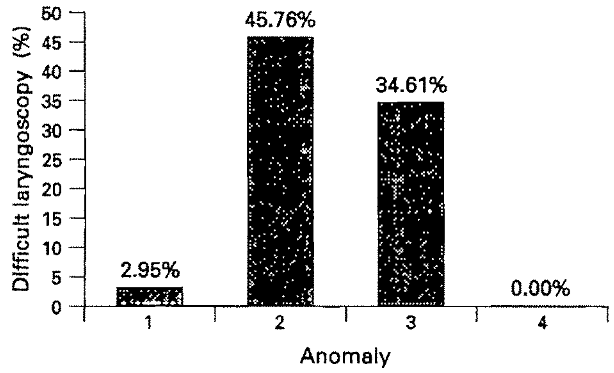


Figure 2 Relationship between anomaly and difficult laryngoscopy. 1 = Unilateral cleft lip, 2 = bilateral cleft lip, 3 = isolated cleft palate with retrognathia and 4 = isolated cleft palate with no retrognathia.

Table 1 Frequency of laryngoscopic views in relation to the age of the patient (number of patients)

	Laryngoscopic view				
Age	I	II	III	IV	Total
0–6 mth	150	161	35	4	350
6–12 mth	80	78	11	1	170
1–5 yr	155	31	5	3	194
5–8 yr	78	8	0	0	86
Total	463	278	51	8	800

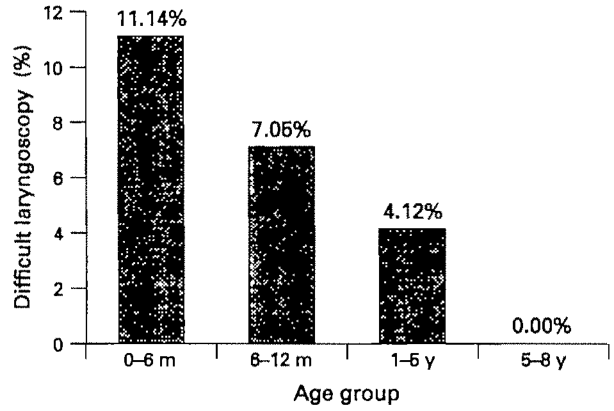


Figure 3 Relationship between age and laryngoscopic view.

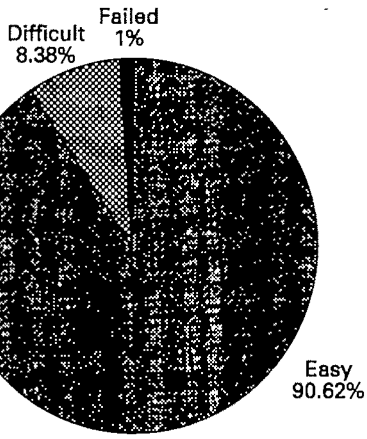


Figure 4 Distribution of ease of tracheal intubation.

Table 2 Ease of tracheal intubation in relation to laryngoscopic view (number of patients)

Laryngoscopic view	Tracheal intubation			
	Easy	Difficult	Failed	Total
I	459	3	0	462
II	266	13	0	279
III	0	48	3	51
IV	0	3	5	8
Total (%)	725 (90.62)	67 (8.38)	8 (1)	800

Table 3 Adverse outcomes with laryngoscopy and intubation

Adverse outcome	No. of patients (%)
Airway bleeding	21 (3)
Pulmonary aspiration of blood	5 (0.6)
Arterial oxygen desaturation < 94%	6 (0.8)
Bradycardia (< 80 beat min^{-1})	9 (1)
Oesophageal intubation	7 (0.9)

(fig. 3). Laryngoscopy was not difficult in children more than 5 yr of age.

Figure 4 shows the distribution of ease of tracheal intubation. Table 2 shows the distribution of ease of tracheal intubation in relation to laryngoscopic view. Tracheal intubation was easy in the majority (90.62%) of patients. All had a grade I or II view. Intubation was difficult in 67 (8.38%), of whom 51 (76.12%) had a grade III or IV view and 16 (23.88%) a grade I or II view. Intubation failed in eight patients (1%); all had a grade III or IV laryngoscopic view and were less than 6 months of age. Four had bilateral cleft lip and alveolus with protruding premaxilla and the remaining four had cleft palate with retrognathia.

Table 3 shows the adverse outcomes associated with laryngoscopy. There was no loss of airway control or any postoperative airway problems. There was no significant decrease in Sp_{O_2} or change in heart rate during laryngoscopy or intubation.

Discussion

In these patients, the airway was patent and not compromised, and the larynx was inaccessible and difficult to view because of various anatomical anomalies. The incidence of difficult laryngoscopy was 7.38%. Comparison with other published reports is difficult because of differences in definition

[9–12]. The age groups and mitigating factors (use of neuromuscular blockers, type of laryngoscope blade) also differed between studies.

The use of optimal laryngeal pressure improves the laryngoscopic view and increases the intubation angle in high anterior larynx. The incidence of grade III view is reduced from 9 % to 5.4–1.3 % by routine use of external laryngeal pressure [13].

Difficult laryngoscopy was not synonymous with difficult intubation. The incidence of failed intubation was only 1 %. Poor outcome with failed or difficult tracheal intubation was avoided by maintenance of spontaneous ventilation and adequate ventilation with face mask and airway in between attempts. There was no instance of "cannot intubate and cannot ventilate by mask", the reported incidence of which is 0.001–0.02 % [9].

In summary, extensive clefts, retrognathia and age less than 6 months were found to be associated with difficult laryngoscopy. These factors must be considered in planning the anaesthetic technique. Where difficulty is anticipated, senior skilled personnel should be present.

Acknowledgements

I thank J. I. L. B. Ratnayake, Faculty of Agriculture, University of Peradeniya, for statistical analysis.

References

1. Department of Health. *Report on Confidential Enquiries into Maternal Deaths in England and Wales 1982–1984*. London: Her Majesty's Stationery Office, 1989; Report on Health and Social Subjects, 34.
2. King TA, Adams AP. Failed tracheal intubation. *British Journal of Anaesthesia* 1990; **65**: 400–414.
3. Patil VU, Stehling LC, Zaunder HL. *Fibre-optic Endoscopy in Anaesthesia*. Chicago: Year Book Medical Publishers, 1983.
4. Mallampati SR, Gatt SP, Gugino LD, Desai SP, Wraksa B, Freiburger D, Liu PL. A clinical sign to predict difficult tracheal intubation: a prospective study. *Canadian Anaesthetists Society Journal* 1985; **32**: 429–434.
5. Wilson ME, Spiegelhalter D, Robertson JA, Lesser P. Predicting difficult intubation. *British Journal of Anaesthesia* 1988; **61**: 211–216.
6. Oates JDL, Macleod AD, Oates PD, Pearsall FJ, Howie JC, Murray GD. Comparison of two methods for predicting difficult intubation. *British Journal of Anaesthesia* 1991; **66**: 305–309.
7. Charters P, Perera S, Horton WA. Visibility of pharyngeal structures as a predictor of difficult intubation. *Anaesthesia* 1987; **42**: 1115.
8. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; **39**: 1105–1111.
9. Benumof JL. Management of the difficult airway with special emphasis on awake tracheal intubation. *Anesthesiology* 1991; **75**: 1087–1110.
10. Samsoon GLT, Young JRB. Difficult tracheal intubation: a retrospective study. *Anaesthesia* 1987; **42**: 487–490.
11. American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Practice guidelines for management of the difficult airway. *Anesthesiology* 1993; **78**: 597–602.
12. Cohen MM, Rose DK. The airway: problems and predictions in 18,500 patients. *Canadian Journal of Anaesthesia* 1994; **41**: 372–383.
13. Westhorpe RN. The position of the larynx in children and its relationship to the ease of intubation. *Anaesthesia and Intensive Care* 1987; **15**: 384–388.

British Journal of Anaesthesia 1996; **76**: 760–766

Volumetric analysis of aeration in the lungs during general anaesthesia

A. REBER, G. ENGBERG, B. SPORRE, L. KVIELE, H.-U. ROTHEN, G. WEGENIUS, U. NYLUND AND G. HEDENSTIERNA

Summary

Spiral computed tomography (CT) allows volumetric analysis of formation of atelectasis and aeration of the lungs during anaesthesia. We studied 26 premedicated patients undergoing elective surgery allocated to group 1 (conscious, spontaneous breathing, investigating inspiration and expiration), group 2 (general anaesthesia with mechanical ventilation, investigating inspiration and expiration) or group 3 (general anaesthesia with mechanical ventilation, investigating changes over time). Using spiral CT, the lungs were studied either before or during general anaesthesia. CT scans were grouped into the following areas: overaeration, normal aeration, reduced aeration, poor aeration and atelectasis. The mechanism of atelectasis appeared to be both gravitational forces and a diaphragm-related force that acts regionally in caudal lung regions. Mean atelectasis formation and poorly aerated regions comprised approximately 4% of the total lung volume between the diaphragm and carina, giving a mean value of 16–20% of the normal aerated lung tissue being either collapsed or poorly aerated. The vertical ventilation distribution was more even during anaesthesia than in the awake state. (*Br. J. Anaesth.* 1996; **76**: 760–766).

Key words

Anaesthesia, general. Lung, atelectasis. Measurement techniques, tomography. Ventilation, mechanical.

It has been shown in previous studies that approximately 90% of all patients who are anaesthetized develop atelectasis in dependent lung regions, that is in the dorsal area of the lungs with the patient in the supine position [1]. Decreases in arterial oxygen tension and increases in the magnitude of shunt correlate with the size of the atelectasis [2, 3]. It can be concluded therefore that formation of atelectasis is a major cause of gas exchange impairment during general anaesthesia [4, 5]. The distribution of atelectasis can assist in elucidating the causative mechanisms. This has not been investigated previously except for the limited analysis performed by single or double exposures through the chest [6]. Volumetric analysis can be achieved using spiral computed tomography (CT) enabling continuous exposure of the lungs while the patient moves slowly through the gantry of the CT scanner [7]. Continuous volume acquisition followed by multiplanar reconstructions makes it possible to detect more details than with standard CT, especially in the lung, while at the same time determining more exactly the relationship of collapsed lung tissue to the surrounding structures.

In this study, we have investigated, by means of volumetric scanning, the changes which occur in the regional variation of aeration and regions of atelectasis formation in the lungs during general anaesthesia and mechanical ventilation. Furthermore, the contribution of diaphragm displacement to tidal ventilation was evaluated using measurements of functional residual capacity and chest–abdomen movement.

Patients and methods

The study was approved by the Ethics Committee of the University Hospital of Uppsala, and written informed consent was obtained from each patient. We studied 26 consecutive patients, ASA I or II, without cardiopulmonary diseases undergoing elective general, neurological or eye surgery (table 1). The refusal rate was 15%. Patients were allocated to group 1 ($n = 6$: premedicated, conscious patients breathing spontaneously, investigating inspiration and expiration), group 2 ($n = 10$: general anaesthesia with mechanical ventilation, investigating inspiration and expiration) or group 3 ($n = 10$: general anaesthesia with mechanical ventilation, investigating delayed changes after 60 min). Three separate groups were investigated in order to limit the radiation exposure to individual patients. The numbers of spiral CT were therefore restricted to two in each patient (see below).

Premedication comprised ketobemidone (Ketogan Novum) 0.07 mg kg^{-1} i.m. Patients were transported

---

ADRIAN REBER*, MD, DEAA, Department of Anaesthesiology and Intensive Care, and Department of Clinical Physiology, University Hospital, Uppsala, Sweden and Department of Anaesthesia, University of Basel/Kantonsspital, Basel, Switzerland. GRETA ENGBERG, MD, PHD, BENGT SPORRE, MD, LENNART KVIELE, MD, HANS-ULRICH ROTHEN, MD, PHD (Department of Anaesthesiology and Intensive Care); GÖRAN WEGENIUS, MD, PHD (Department of Radiology); ULF NYLUND (Department of Medical Technology); GÖRAN HEDENSTIERNA, MD, PHD (Department of Clinical Physiology); University Hospital, Uppsala, Sweden. Accepted for publication: February 15, 1996.

*Address for correspondence: Department of Clinical Physiology, University Hospital, S-751 85 Uppsala, Sweden.

Table 1 Patient data (mean (SD) [range] or number). BMI = Body mass index (weight height^2). Kruskal–Wallis ANOVA (= analysis of variance)

	Group 1	Group 2	Group 3	ANOVA
Study conditions for spiral CT	Conscious, spontaneous breathing, inspiration/expiration	Anaesthesia, mechanical ventilation, inspiration/expiration	Anaesthesia, mechanical ventilation, 10 *vs* 60 min: scans at FRC	$P = 0.05$
Sex (M/F)	5/1	7/3	5/5	
Age (yr)	52 [37]	47 [40]	50 [32]	ns
BMI (kg m^{-2})	26.4 (1.9) [4.7]	25.2 (3.1) [10.9]	25.4 (2.8) [9.8]	ns
Smoker/non-smoker	2/4	3/7	3/7	

to the X-ray department and positioned supine on the CT table. In group 1, spiral CT were performed in the premedicated, conscious patient before induction of general anaesthesia. In groups 2 and 3, general anaesthesia was induced with propofol 1–2 mg kg^{-1} and fentanyl 0.002 mg kg^{-1}, and muscular paralysis was produced with pancuronium 0.1 mg kg^{-1}. After intubation of the trachea, anaesthesia was maintained with a continuous infusion of propofol 6–8 mg kg^{-1} h^{-1} and fentanyl injections (0.05–0.1 mg) as necessary.

The lungs were ventilated mechanically at a rate of 12–14 bpm with 40% oxygen in nitrogen (FI_{O_2} 0.4) with a Servo Ventilator 900D or 710 (Siemens-Elema, Stockholm, Sweden). Minute volume was adjusted by changing *f* (frequency) to maintain end-tidal carbon dioxide concentration ($P\text{CO}_2$) at 4.5 and 4.9 kPa (CO_2 analyzer 5250 RGM, BOC Ohmeda, Louisville, CO, USA) with a tidal volume of 8 ml kg^{-1}. No additional changes in ventilation were made during the 60-min study.

SPIRAL CT OF THE LUNGS

Aeration of the lungs and distribution of atelectasis (see below) were studied by spiral CT of the lungs (Somatom plus, Siemens, Erlangen, Germany). Patients lying in their bed supine were lifted onto the CT table and the mean time between reclining on the table and the CT being undertaken was 30 min. Patients lay in the supine position with the arms alongside the body [8] while slowly moving through the gantry during exposure. While awake (group 1) or 10 min after induction of anaesthesia (groups 2 and 3), a frontal scout-view covering the chest was performed at end-expiration to define the borders of the lungs and to guide the settings of the succeeding spiral CT. The spiral CT were obtained during 10 s of breath-holding at end-expiration and end-inspiration in groups 1 and 2, covering the basal region of the lungs. In group 3, spiral CT were obtained during 20 s of breath-holding at end-expiration (= 0 airway pressure) from the left (= lower) most cephalad point of the diaphragm at least as far as the carina and further cranially, depending on the lung distance in each individual patient. There was a delay of 3 s before starting the spiral CT, allowing full expiration. The additional spiral settings were as follows: table speed 8 mm s^{-1}, 120 kVp tube voltage and 125 mA current, 8 mm slice thickness. After investigation, the scans were reconstructed in 4-mm increments. In group 3, a second spiral CT was performed 60 min after induction of anaesthesia. The maximum total amount of radiation (quantity) any patient received was 5 mSv, which does not exceed the effective dose equivalent per year for Swedish citizens. After the investigation, patients were transported to the operating theatre for surgery.

ANALYSIS OF THE SPIRAL CT SLICES

The interpolated, uncompressed 512 × 512 matrix scans, consisting of picture elements (pixels) of approximately 0.9 × 0.9 mm, were transposed to an 8-bit TIFF format (256 Gy values). Thus images were rendered legible for the image analysis software package Optimas, version 4.1 (Bioscan Inc, Edmonds, WA, USA). For each scan, the left and right lung contours were traced using a semi-automatic technique [9]. If possible, automatic tracing by an algorithm based on the standard formula for polygonal areas was performed. Manual tracing by eye, drawing the external boundary along the inside of the ribs and the internal boundary along the mediastinal organs (excluding large structures of the hilus) was performed if necessary to mask lung tissue densities. The following regions of interest (ROI) were studied: in groups 1 and 2, inspiratory and expiratory scans at a level just above the diaphragm dome were evaluated. Appropriate inspiratory and expiratory scans were chosen by identifying key anatomical landmarks in both. Thus the position of the scan with regard to the spine differed between scans. The vertical height of the basal CT section was measured as the distance between the ventral and dorsal surface of the lung. The section was divided vertically into five equal levels. Level 1 refers to the most ventral level and level 5 to the most dorsal, as modified from the method of Gattinoni and co-workers [10]. The attenuation values were measured in each interval in both the expiratory and inspiratory scans.

In group 3, the lung was divided into five areas, corresponding to the following attenuation values: −1000 to −900 Hounsfield units (HU) (over-aerated) [11], −900 to −500 HU (normal aeration), −500 to −200 HU (reduced aeration) (modified from [12]), −200 to −100 HU (poor aeration) and −100 to +100 HU (attenuation values corresponding to atelectasis) [13].

In one patient, a three-dimensional image was built up with an additional imaging software package (3 DE-Editor and 3 DE-viewer, Maidenhead.

CONTRIBUTION OF THE DIAPHRAGM TO TIDAL VENTILATION

In group 3, ventilation was partitioned into rib cage and abdomen–diaphragm components by respiratory inductive plethysmography (RIP) before and during general anaesthesia [14, 15]. The signals from the RIP were recorded on a microprocessor system (Respitrace, non-invasive monitoring systems, Miami Beach, FL, USA). Additionally, functional residual capacity (FRC) was measured during anaesthesia and mechanical ventilation by a multiple breath wash-in-wash-out sulphur hexafluoride (SF$_6$) technique according to Larsson and co-workers [16].

DATA TRANSFORMATION AND STATISTICAL ANALYSIS

The areas of different attenuation numbers at a given level (as indicated above) were expressed as percentages of the total lung parenchyma (cross-sectional area of the thorax excluding the chest wall and the manually traced hilar structures) to take into account the difference in quantity of lung tissue between basal and apical scans. Analysis of levels within the well defined region between the most cephalad point of the diaphragm (= base) and the carina, defined as 100% distance from the diaphragm, enabled comparison of regional variabilities of the patient's lungs. Thus an accurate volumetric comparison of the same lung regions was performed in different patients. As an appropriate transformation for percentage values, the arcsine of the square root of the mean was calculated for statistical analysis [17].

Unless otherwise stated, values are mean (SD) and range. In addition, 95% confidence intervals are given where appropriate. To compare data within groups, the Wilcoxon signed rank test and Friedman's analysis of variance (ANOVA) were used. For *post hoc* comparisons, Tukey's test was applied and probability values were calculated. To compare data between the groups, the Kruskal–Wallis ANOVA and the Wilcoxon rank sum test were used. Spearman's rank correlation coefficient (r_s) was used to analyse the relationships between variables. For all calculations, the Statistica/w 4.5 software package (StatSoft, Tulsa, OK, USA) was used.

Results

CONSCIOUS, SPONTANEOUSLY BREATHING AFTER PREMEDICATION

All lung densities were observed. However, regions with attenuation < -900 HU occurred only in one patient. They were located in the upper, non-dependent region and varied between 3% in the apex and up to 11% at the base. Few (less than 1%) areas with attenuation values of between -200 and $+100$ HU were scattered through the most dependent region of the lungs.

The mean expiratory attenuation value was -658 (SD 103) HU and the mean inspiratory value -789 (74) HU. Dependent lung regions showed more than twice as large variation in the attenuation during respiration than in non-dependent lung regions (fig. 1 (left panel), table 2). Assuming a gas distribution in proportion to the attenuation changes (expressed in HU), an almost two-fold increase in ventilation was calculated for the dorsal lung region, compared with the ventral, non-dependent one (table 2).

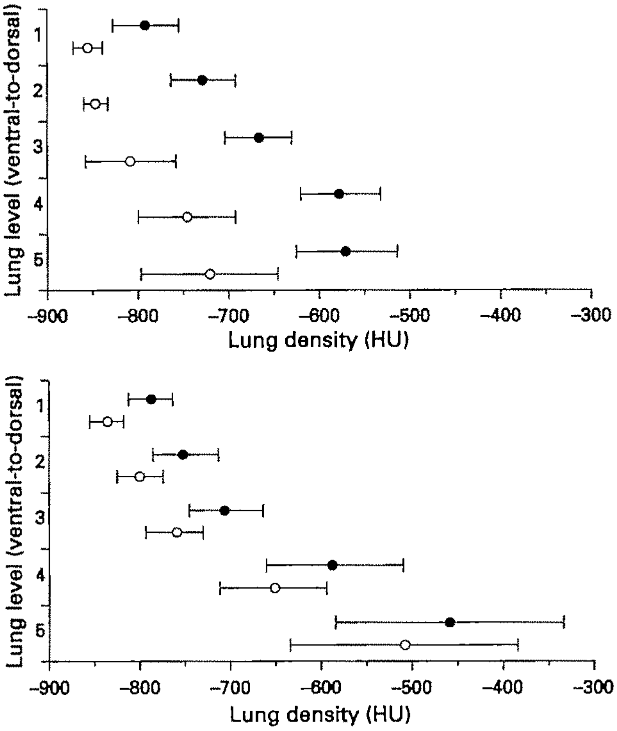


Figure 1 Distribution of ventilation in conscious, spontaneously breathing patients (top) and in patients 10 min after induction of anaesthesia (bottom) (mean, SD). Note the dorsoventral distribution of mean attenuation values (in Hounsfield units (HU)) in inspiration (○) and expiration (●). Data from the right lung are included (left lung is not shown but displayed similar values).

AERATION 10 MIN AFTER INDUCTION OF ANAESTHESIA

Densities defined as atelectasis were distributed over the whole distance between the diaphragm and the carina (fig. 2). However, atelectasis was larger in the basal part of the lung ($P < 0.05$) and decreased with increasing distance from the diaphragm ($r_s = -0.43$). In five patients, spiral CT included nearly the whole lung, from the diaphragm to the apex. In these patients, measurements of formation of atelectasis in more cranial parts of the scans were less reliable because of increasing scatter close to the rib cage. However, no or only small amounts of atelectasis (less than 0.5%) were detected in these regions. A significantly larger amount of attenuation values between -200 and -100 HU in dependent lung regions was found during anaesthesia compared with awake ($P < 0.05$) (table 2). These regions were of similar magnitude to those with atelectasis, and were located above the atelectatic areas. They also decreased in size with increasing distance from the diaphragm ($r_s = -0.38$). Regional analysis of accumulated data from the different slices showed the following: the quantity of both atelectatic and poorly aerated regions in the basal region (0–40% distance from the diaphragm) was significantly larger

Table 2 Increase in lung attenuation from inspiration to expiration (supine position) (mean (SD))

		Conscious, spontaneous breathing		Anaesthesia, mechanical ventilation	
Level	Lung	Increase (HU)	Distribution of ventilation (%)	Increase (HU)	Distribution of ventilation (%)
1	R	64 (41)	13	48 (19)	18
	L	93 (43)	13	51 (26)	17
2	R	118 (18)	17	50 (20)	19
	L	108 (79)	14	70 (36)	24
3	R	128 (11)	18	59 (23)	21
	L	121 (88)	17	56 (25)	19
4	R	170 (97)	28	67 (32)	24
	L	167 (84)	31	69 (39)	22
5	R	152 (109)	24	49 (29)	18
	L	179 (113)	25	48 (40)	18
All	R	127 (83)	100	54 (25)	100
	L	134 (84)	100	59 (33)	100

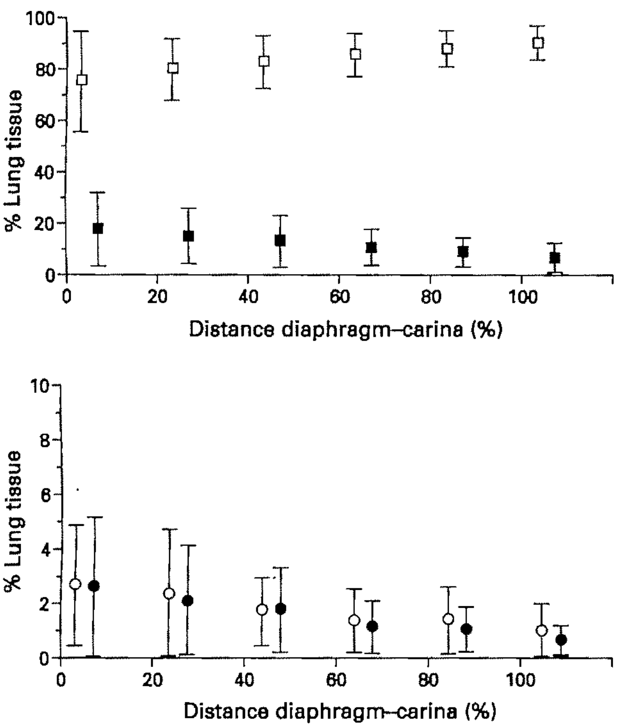


Figure 2 Aeration in the lungs between the diaphragm and the carina 10 min after induction of anaesthesia. The means (SD) for the areas with different densities are presented: values for normal (□) and reduced (■) aeration (top) and values for poor aeration (○) and atelectasis (●), (bottom). Data from the left and right lung are included.

than in the apical zone (60–100 % distance from the diaphragm) ($P < 0.05$). There was no correlation between atelectasis formation and height of the lung in the sagittal plane, cross-sectional height of the lung, body mass index, age, sex or smoking habit. There were no significant differences between the right and left lungs.

Areas with aeration between −500 and −900 HU were significantly more common in the apical region compared with the basal region ($P < 0.05$) (fig. 2). The correlation between the amount of densities between −200 and −900 HU and the distance from the diaphragm was calculated as $r_s = 0.46$ for densities between −500 and −900 HU ($P < 0.01$) and $r_s = -0.36$ for densities between −200 and −500 HU ($P < 0.01$). There was no significant difference in aeration between left and right lungs. FRC after 10 min of anaesthesia was 1390 (320) ml.

VENTILATION DURING ANAESTHESIA

In group 2, during anaesthesia, attenuation varied to a significantly lesser extent for the whole lung field than in the conscious subjects (group 1) ($P < 0.05$). Thus mean expiratory attenuation was −660 (140) HU, and the inspiratory value was −714 (136) HU (for inspiratory values, $P < 0.05$ compared with awake findings; no significant difference for expiratory values). The changes in attenuation over tidal volume were more similar over the lung field than in the awake state, with only a minor and insignificant increase from the ventral- to the dorsal-dependent segments (table 2). Attenuation values expressed as distribution of ventilation showed no significant difference between dependent and non-dependent segments. Thus ventilation was evenly distributed in the vertical, gravitational direction.

Table 3 Clinical data (time course). Data are mean (95 % confidence interval). For FRC comparisons, Wilcoxon matched pairs test: ns; for %RC comparisons, Friedman–ANOVA test: $^{**}P < 0.01$

	Conscious, spontaneous breathing	Anaesthesia, mechanical ventilation	
		10 min	60 min
FRC (10 *vs* 60 min)		1390 (1180–1610)	1430 (1190–1670)
%RC	41 (30–51)**	61 (52–69)	61 (52–70)
Distance (% of lung height) diaphragm – carina right/left		52 (49–55)/57 (53–62)	

The contribution of rib cage excursions to ventilation was significantly higher compared with the awake situation (61 (13)% *vs* 41 (15)%).

AERATION 60 MIN AFTER INDUCTION OF ANAESTHESIA

In group 3, there was no significant change in the amount or distribution of atelectasis or gas content when comparing lungs 10 and 60 min after induction of anaesthesia. There was no significant difference between left and right lungs. Mean FRC 60 min after induction was 1460 (350) ml and the mean percentage contribution of rib cage excursions to ventilation was 61 (13)%, and thus similar to the values after 10 min of anaesthesia (table 3).

Discussion

A volumetric approach to analysis of the lungs during general anaesthesia using spiral CT enables a more comprehensive description of aeration compared with one or more single exposures through the chest. The major findings in this study were that atelectasis was distributed from the base to the apex of the lung but was larger in caudal regions. It comprised, on average, 2% of the total lung volume which corresponds to approximately 10% of the normal aerated lung tissue. A similar amount of lung tissue, just above the atelectatic zone, was poorly aerated. Furthermore, ventilation was distributed more evenly from the top to the bottom of the lung (anteroposterior) during anaesthesia compared with the awake state. These findings are discussed below after some methodological aspects.

SPIRAL CT AND ANALYSIS

Conventional CT methods using multiple exposures through the chest, one after the other, with a time delay between, can lead to errors caused by differences in the depth of breathing and respiratory movements. Performing spiral CT leads to a reduction in these problems. Spiral CT implies volumetric scanning of the entire lung volume in a single breath hold and enables reconstruction of images at any chosen interval which results in improved detection of tissue and gas distribution. The total quantity of radiation is a limiting factor, and allows only two spiral CT with the settings described above. Despite not covering the entire lung distance in all patients, the most important areas of the lungs were analysed. Analysing the lungs caudal to the most cephalad point of the diaphragm was less reliable when scans included lung tissue and diaphragm. Partial volume effects of the diaphragm were enhanced by the additional transformations for image analysis [18]. Similar problems occurred between the carina and the apex, with scatter effects along the rib cage.

ATELECTASIS AND REGIONS WITH POOR AERATION

During anaesthesia, mean atelectasis formation in dependent lung regions was approximately 2% of the total lung volume between the diaphragm and the carina, as measured by spiral CT. As the amount of lung tissue per pixel element is four to five times larger in the atelectatic area than in aerated lung tissue in non-dependent parts of the lungs [6], the observed mean amount of atelectasis corresponds to 8–10% of the whole lung. A similar quantity of areas with poor aeration was seen, giving a mean value of 16–20% of the lung tissue being either collapsed or poorly aerated. These regions make a major contribution to shunt and regions with low ventilation–perfusion ratios ($\dot{V}\text{A}/\dot{Q}$), which have been shown in previous studies [19, 20]. During inhalation anaesthesia, shunt and perfusion of poorly ventilated lung regions (low $\dot{V}\text{A}/\dot{Q}$) have been estimated previously at 4–5% each [19]. The smaller perfusion values of these regions are reasonably explained by hypoxic pulmonary vasoconstriction (HPV) which still prevails, despite the use of anaesthetic agents. It has been shown by Marshall, Lindgren and Marshall that inhalation anaesthetics depress HPV by 20–30% at 1.0 MAC [21].

A progressive decrease in the amount of atelectasis was noted from the diaphragm to the apex, an observation suspected in previous studies using two or three CT scans through the chest [5, 19]. This finding is interesting in that it suggests another mechanism besides gravity. The latter reasonably explains the increased atelectasis in dependent regions but cannot explain the observed increase in atelectasis in regions near the diaphragm. Rather, relaxation of the diaphragm, and subsequent compression and collapse of underlying lung tissue, could be responsible for this non-homogeneous distribution of atelectasis and poorly aerated areas. This was suspected in earlier studies which observed rapid formation of atelectasis on induction of anaesthesia and on discontinuation of PEEP [1], and decreases in atelectasis after contraction of the diaphragm during phrenic nerve stimulation [22]. Also, the decrease in diaphragm movement during mechanical ventilation and muscle paralysis may be another factor that promoted atelectasis formation in dependent lung regions close to the diaphragm.

AERATION OVER TIME

We paid special attention to the differential aeration of the lung tissue as it may provide more information about the dynamics of the transition between aerated and collapsed lung regions. We believed that poorly aerated areas with attenuation values between −200 and −100 HU would be converted to atelectasis during the 60 min of anaesthesia that followed. However, none of these areas was altered in size or distribution over time. This suggests that areas with poor aeration remained stable during the observation period. These findings are supported by the unchanged FRC with time. The rapid development of densities after induction of anaesthesia contrasts with the lack of progression later in time. However, an additional increase in atelectasis during anaesthesia can be seen if the inspiratory gases are highly soluble in blood, as during oxygen–nitrous oxide anaesthesia [19], and ventilation with 100% oxygen [23].

VENTILATION DISTRIBUTION

The uneven distribution of ventilation in the awake subject with more air going to dorsal, dependent lung regions, has been shown previously in several studies using isotope techniques [24, 25]. The vertical inhomogeneity was proposed by Milic-Emili and co-workers to be caused by regional differences in pleural pressures [26].

Ventilation was affected significantly by anaesthesia and mechanical ventilation, with gas being more evenly distributed from the ventral to the dorsal parts of the lungs while patients were in the supine position. Rehder, Sessler and Rodarte demonstrated a similarly different distribution of ventilation during anaesthesia, using an isotope technique [27]. They suggested that altered ventilation was caused by changes in the shape of the chest wall. That such changes occur have been demonstrated by CT [28]. Krayer and co-workers used high-speed CT that enabled breath-by-breath analysis, providing evidence that changes in thoraco–abdominal motion could explain the altered ventilation distribution during anaesthesia [29].

The findings of atelectasis in dependent lung regions [1] and airway closure [30] during anaesthesia can also explain the impeded ventilation in dependent lung regions. However, the more even distribution of ventilation need not indicate a better ventilation–perfusion ratio, as perfusion is switched towards dependent lung regions which may cause or enhance ventilation–perfusion inequality [31, 32]. Also, poor ventilation of dependent regions may promote atelectasis formation by enhancing gas resorption [23, 32]. Furthermore, the increase in the rib cage contribution to tidal volume during mechanical ventilation and muscle paralysis decreases phasic passive diaphragmatic movement. This is in contrast with observations while spontaneous breathing is maintained [20] and may be a factor that promotes atelectasis formation in dependent lung regions close to the diaphragm.

In summary, a volumetric approach to CT analysis of the lungs provides a more complete description of changes in aeration during general anaesthesia. Induction of anaesthesia causes the formation of atelectasis in a gravitationally oriented fashion (i.e. in dependent lung regions), but also with a non-gravitational inhomogeneity (increasing atelectasis from the apex to the base). There is no evidence of change in regional aeration with time during the first hour of anaesthesia. Atelectasis comprises almost 10 % of the lung tissue. Another 8–10 % of the lung tissue, just above the atelectatic zone, is poorly aerated with less than 20 % of the volume being gas. Finally, the vertical ventilation distribution was more even during anaesthesia than in the awake state.

Acknowledgements

We thank the X-ray laboratory team (M. Almgren, L. Haglund and A. Lundberg), U. Wallin for additional assistance in the image analysing procedures and R. Pettersson, Department of Statistics, for statistical advice. We also thank D. Engström and N. Mushet for editorial assistance. Supported by grants from the Swedish Medical Research Council (grant No. 5315) and the Swedish Heart–Lung Fund. A.R. is supported by a fellowship from the Swiss National Foundation for Scientific Research and by the Schweizerische Stiftung für Medizinisch-Biologische Stipendien.

References

1. Brismar B, Hedenstierna G, Lundquist H, Strandberg Å, Svensson L, Tokics L. Pulmonary densities during anesthesia with muscular relaxation—a proposal of atelectasis. *Anesthesiology* 1985; **62**: 422–428.
2. Hedenstierna G, Tokics L, Strandberg Å, Lundquist H, Brismar B. Correlation of gas exchange impairment to development of atelectasis during anaesthesia and muscle paralysis. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 183–191.
3. Tokics L, Strandberg Å, Brismar B, Lundquist H, Hedenstierna G. Computerized tomography of the chest and gas exchange measurements during ketamine anaesthesia. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 684–692.
4. Hedenstierna G. Gas exchange during anaesthesia. *British Journal of Anaesthesia* 1987; **64**: 507–514.
5. Gunnarson L, Tokics L, Gustavsson H, Hedenstierna G. Influence of age on atelectasis formation and gas exchange impairment during general anaesthesia. *British Journal of Anaesthesia* 1991; **66**: 423–432.
6. Hachenberg T, Lundquist H, Tokics L, Brismar B, Hedenstierna G. Analysis of lung density by computed tomography before and during general anaesthesia. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 549–555.
7. Kalender WA, Seissler W, Klotz E, Vock P. Spiral volumetric CT with single-breath-hold technique, continuous transport and continuous scanner rotation. *Radiology* 1990; **176**: 181–183.
8. Lumb AB, Nunn JF. Respiratory function and rib cage contribution to ventilation and body positions commonly used during anesthesia. *Anesthesia and Analgesia* 1991; **73**: 422–426.
9. Kalender WA, Fichte H, Bautz W, Skalej M. Semiautomatic evaluation procedures for quantitative CT of the lungs. *Journal of Computer Assisted Tomography* 1991; **15**: 248–255.
10. Gattinoni L, Pelosi P, Vitale G, Pesenti A, D'Andrea L, Mascheroni D. Body position changes redistribute lung computed tomographic density in patients with acute respiratory failure. *Anesthesiology* 1991; **74**: 15–23.
11. Gould GA, Macnee W, McLean A, Warren PM, Redpath A, Best JJK, Lamb D, Flenley DC. CT measurements of lung density in life can quantitate distal airspace enlargement: an essential defining feature of human emphysema. *American Review of Respiratory Disease* 1988; **137**: 380–392.
12. Gattinoni L, Pesenti A, Bombino M, Baglioni S, Rivolta M, Rossi F, Rossi G, Fumagalli R, Marcolin R, Mascheroni D, Torresin A. Relationships between lung computed tomographic density, gas exchange, and PEEP in acute respiratory failure. *Anesthesiology* 1988; **69**: 824–832.
13. Lundquist H, Hedenstierna G, Strandberg Å, Tokics L, Brismar B. CT-assessment of dependent lung densities in man during general anaesthesia. *Acta Radiologica* 1995; **36**: 626–632.
14. Milledge JS, Scott FD. Inductive plethysmography—a new respiratory transducer. *Journal of Physiology* (*London*) 1979; **267**: 4–5P.
15. Valta P, Takala J, Foster R, Weissman C, Kinney JM. Evaluation of respiratory inductive plethysmography in the measurement of breathing pattern and PEEP-induced changes in lung volume. *Chest* 1992; **102**: 234–238.
16. Larsson A, Linnarsson D, Jonmarker C, Jonsson B, Larsson H, Werner O. Measurement of lung volume by sulfur hexafluoride washout during spontaneous and controlled ventilation: further development of a method. *Anesthesiology* 1987; **67**: 543–550.
17. Berenson ML, Levine DM, Goldstein M. *Intermediate Statistical Methods and Applications*. London: Prentice-Hall, 1983; 69–70.
18. Wegener OH. *Whole Body Computerized Tomography*. New York: Karger, 1983; 1–30/50–1–50.
19. Gunnarsson L, Strandberg Å, Brismar B, Tokics L,

Lundquist H, Hedenstierna G. Atelectasis and gas exchange impairment during enflurane/nitrous oxide anaesthesia. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 629–637.

20. Tokics L, Hedenstierna G, Strandberg Å, Brismar B, Lundquist H. Lung collapse and gas exchange during general anesthesia—effects of spontaneous breathing, muscle paralysis and positive end-expiratory pressure. *Anesthesiology* 1987; **66**: 39–47.
21. Marshall C, Lindgren L, Marshall BE. Effects of halothane, enflurane, and isoflurane on hypoxic pulmonary vasoconstriction in rat lungs in vitro. *Anesthesiology* 1984; **60**: 304–308.
22. Hedenstierna G, Tokics L, Lundquist H, Andersson T, Stransberg Å, Brismar B. Phrenic nerve stimulation during halothane anesthesia. *Anesthesiology* 1994; **80**: 751–760.
23. Rothen HU, Sporre B, Engberg G, Wegenius G, Högman M, Hedenstierna G. Influence of gas composition on recurrence of atelectasis after a reexpansion maneuver during general anesthesia. *Anesthesiology* 1995; **82**: 832–842.
24. West JB, Dollery CT, Naimark A. Distribution of blood flow in isolated lung: relation to vascular and alveolar pressures. *Journal of Applied Physiology* 1964; **19**: 713–724.
25. Hughes JMB, Glazier JB, Maloney JE, West JB. Effect of extra-alveolar vessels on distribution of blood flow in the dog lung. *Journal of Applied Physiology* 1968; **25**: 701–712.
26. Milic-Emili J, Henderson JAM, Dolovich MB, Trop D, Kaneko K. Regional distribution of inspired gas in the lungs. *Journal of Applied Physiology* 1966; **21**: 749–759.
27. Rehder K, Sessler AD, Rodarte JR. Regional intrapulmonary gas distribution in awake and anesthetized-paralyzed man. *Journal of Applied Physiology* 1977; **42**: 391–402.
28. Hedenstierna G, Strandberg Å, Brismar B, Lundquist H, Svensson L, Tokics L. Functional residual capacity, thoracoabdominal dimensions and central blood volume during general anesthesia with muscle paralysis and mechanical ventilation. *Anesthesiology* 1985; **62**: 247–254.
29. Krayer S, Rehder K, Vettermann J, Didier EP, Ritman EL. Position and motion of the human diaphragm during anesthesia-paralysis. *Anesthesiology* 1989; **70**: 891–898.
30. Hedenstierna G, Santesson G. Airway closure during anesthesia: a comparison between resident-gas and argon-bolus techniques. *Journal of Applied Physiology* 1979; **47**: 874–881.
31. Landmark SJ, Knopp TJ, Rehder K, Sessler AD. Regional pulmonary perfusion and V/Q in awake and anesthetized-paralyzed man. *Journal of Applied Physiology* 1977; **43**: 993–1000.
32. Dantzker DR, Wagner PD, West JB. Instability of lung units with low $\dot{V}_A/\dot{Q}$ ratios during O_2 breathing. *Journal of Applied Physiology* 1975; **38**: 886–895.

British Journal of Anaesthesia 1996; **76**: 767–771

Sevoflurane–nitrous oxide or halothane–nitrous oxide for paediatric bronchoscopy and gastroscopy

O. A. MERETOJA, T. TAIVAINEN, L. RÄIHÄ, R. KORPELA AND K. WIRTAVUORI

Summary

We have studied 120 infants and children, in three age groups (3–11 months, 1–5 yr and 6–15 yr), to compare anaesthesia with sevoflurane or halothane for bronchoscopy or gastroscopy, or both. Premedication or i.v. anaesthetic agents were not used. Patients were allocated randomly to receive either 7% sevoflurane or 3% halothane in 66% nitrous oxide in oxygen for induction of anaesthesia. The same inspired mixture was continued during bronchoscopy while the concentration of the inhalation agent was reduced by 50% during gastroscopy. Induction times were shorter for infants than for children and shorter for sevoflurane than for halothane. Cardiac arrhythmias were significantly more frequent during halothane than during sevoflurane anaesthesia. Physiological and psychomotor recovery were more rapid after sevoflurane than after halothane. At 24-h follow-up, children who received sevoflurane had significantly less nausea and vomiting. We conclude that sevoflurane was superior to halothane for paediatric bronchoscopy and gastroscopy. (*Br. J. Anaesth.* 1996; **76**: 767–771)

Key words

Anaesthesia, paediatric. Anaesthetics volatile, halothane. Anaesthetics volatile, sevoflurane. Surgery, endoscopy. Children. Infants.

Paediatric bronchoscopy requires a deep level of anaesthesia of relatively short duration. Spontaneous breathing can be maintained if an inhalation anaesthetic is used and neuromuscular blockers are avoided. Paediatric gastroscopy also requires general anaesthesia and in most cases tracheal intubation. For this purpose inhalation anaesthesia can be used successfully if relatively high anaesthetic concentrations are used for tracheal intubation. We could not find any studies comparing different anaesthetic methods for paediatric endoscopies even though paediatric anaesthesia textbooks give recommendations [1–4]. Halothane has been the classic inhalation anaesthetic for paediatric patients, while sevoflurane has challenged its use recently in general surgery [5–9]. We have therefore compared sevoflurane–nitrous oxide to halothane–nitrous oxide anaesthesia in 120 infants and children for bronchoscopy and gastroscopy.

Patients and methods

After obtaining institutional Ethics Committee approval and written parental consent, we studied 120 ASA I–III boys and girls undergoing elective bronchoscopy, gastroscopy, or both. Patients were stratified into three age groups of 40: infants 3–11 months old, young children 1–5 yr old and older children 6–15 yr old. Exclusion criteria were unusual response to halogenated inhalation agents and significant cardiovascular, pulmonary, hepatic, renal or muscular disease.

No premedication was used. Anaesthesia was administered at one of two sites: the outpatient department where parents were present during induction of anaesthesia (52 children older than 1 yr), or the operating theatre. Anaesthesia, was administered by one of the staff anaesthetists with 4–14 years' full-time experience of paediatric anaesthesia. Before induction of anaesthesia, a sealed envelope was opened to allocate patients randomly to receive either sevoflurane or halothane anaesthesia. The inspired concentrations of these agents were approximately equipotent [10, 11]. An independent observer recorded all times and events during and after anaesthesia. The anaesthesia breathing system was either a Jackson-Rees T-piece (patients with a body weight of less than 30 kg) or a Bain system with a fresh gas flow equal to the square root of body weight. Induction of anaesthesia was commenced with inhalation of 66% nitrous oxide in oxygen and 7% sevoflurane or 3% halothane via a transparent silicone face mask applied at the end of a spontaneous expiration. If the children co-operated, they were asked to take a deep breath and maximal exhalation and then a mask was placed gently on the face. When consciousness was lost, an i.v. cannula was inserted and Ringer's acetate solution infused at a rate of 3–4 ml kg^{-1} h^{-1}. During induction of anaesthesia, spontaneous breathing was maintained and the time from application of the face mask to loss of the eyelash reflex (time to loss of eyelash reflex) and until the child had regular breathing and forward directed constricted pupils (time to end of induction) were recorded. Thereafter, tracheal intubation was per-

---

O. A. MERETOJA, MD, PHD, T. TAIVAINEN, MD, PHD, L. RÄIHÄ, RN, R. KORPELA, MD, K. WIRTAVUORI, MD, Department of Anaesthesiology, Children's Hospital University of Helsinki, FIN-00290 Helsinki, Finland. Accepted for publication: January 22, 1996.

Correspondence to O. A. M.

formed or, in the case of bronchoscopy, a rigid bronchoscope (with a side-arm attachment for fresh gas) was introduced. No topical anaesthetics were used.

Inspired concentrations of sevoflurane or halothane were maintained unchanged during bronchoscopy and reduced by 50% during gastroscopy. At completion of endoscopy, nitrous oxide and the inhalation agent were discontinued simultaneously and the tracheal tube or bronchoscope removed. Thereafter, the child was taken to a postanaesthetic recovery unit until fully awake. Times from discontinuation of sevoflurane or halothane until the patient moved or responded to a non-painful stimulus (emergence time), and until the patient stated his or her name (time to orientation) were recorded.

Patient recovery was assessed at 10-min intervals by a modified Aldrete score according to which patients receive 0–10 points, that is 0–2 points for five physiological variables (motor activity, respiration, circulation, consciousness and temperature) with 2 points for each variable indicating full normal activity [12]. Patients were regarded as ready to be discharged from the recovery room when they scored 8 or more and communicated normally (time to discharge). In addition, psychomotor recovery in the oldest age group of patients ($\geq$ 6 yr old) was tested using the Trieger dot at 15-min intervals. In this simple pen and paper test, children connected as many dots as possible in 10 s, with the maximum number of points being 52. The results of this test were compared with individual pre-anaesthetic performance. If patients were too sleepy or tired, or had poor co-ordination which prevented them from performing the Trieger dot test, their points were taken as 0 at these times.

Routine patient monitoring included non-invasive arterial pressure, heart rate, oxygen saturation (Cardiocap, Datex, Finland), inspired and expired sevoflurane or halothane, and carbon dioxide measurement (Capnomac Ultima, Datex, Finland). Any untoward effects (e.g. cough, laryngeal spasm, breath-holding or excitement) were recorded. Most patients were outpatients and left for home within 2 h from the end of anaesthesia, while some patients remained in hospital for surgical reasons.

Patients were reviewed 24 h after anaesthesia by telephone call or by personal visit, for the incident of nausea and vomiting or other side effects during the 24-h post-anaesthetic period. In addition, a standard questionnaire was used to enquire about acceptance of induction of anaesthesia (a written question "How would you describe the experience when you lost consciousness?") graded as pleasant, indifferent, or unpleasant, and if a child would like a future anaesthesia carried out in the same way (a written question "Would you like to have the same anaesthetic administered if you return to hospital for further surgery?"). The answers to these questions were obtained from children, and in the event that they could not express an opinion themselves because of their young age, from their parents who were present during induction of anaesthesia.

For statistical analyses, a two-tailed unpaired Student's t test was used for patient characteristics. All induction and recovery data within one anaesthesia group were compared by a Kruskal–Wallis test followed by Mann–Whitney U tests. Between-group comparisons were made by a Mann–Whitney U test and the incidence of side effects by Fisher's exact test. Data are expressed as mean (SD) for patient characteristics and as median (10–90 percentile range) for induction and recovery data. $P < 0.05$ was regarded as statistically significant.

Results

Patient characteristics and duration of inhalation anaesthesia were similar for the two groups (table 1). Induction of anaesthesia was significantly shorter in patients anaesthetized with sevoflurane compared with halothane in the three age groups (table 2). Times to end of induction were shorter in infants than in older children for both anaesthetic groups.

Children in the sevoflurane group had a significantly lower incidence of clinically important side effects than those in the halothane group (table 3). The most frequent side effect was cardiac arrhythmia in 17 children (19 separate episodes). Two patients in the halothane group experienced two separate arrhythmias that were more than 10 min apart, and one patient in the halothane group experienced bigeminy during anaesthesia and laryngeal spasm after extubation.

Recovery from anaesthesia was significantly more rapid after sevoflurane than after halothane anaesthesia in all age groups (table 2). Time to recovery was similar in all age groups during sevoflurane

Table 1 Patient characteristics and clinical data (mean (SD or range) or number of patients). No significant differences between groups

	Sevoflurane (n = 60)	Halothane (n = 60)
3–11 months old		
Age (months)	7.0 (9.0–11.0)	6.2 (3.0–10.9)
Weight (kg)	7.5 (1.3)	7.9 (1.6)
Duration of anaesthesia (min)	17.0 (8.0)	18.4 (7.4)
Type of surgery		
Bronchoscopy	8	4
Bronchoscopy and gastroscopy	3	9
Gastroscopy	9	7
1–5 yr old		
Age (yr)	3.1 (1.1–5.8)	3.0 (1.2–5.5)
Weight (kg)	15.4 (5.5)	14.2 (3.1)
Duration of anaesthesia (min)	16.7 (5.0)	18.8 (6.1)
Type of surgery		
Bronchoscopy	2	3
Bronchoscopy and gastroscopy	5	4
Gastroscopy	13	13
6–15 yr old		
Age (yr)	11.4 (6.8–14.9)	10.5 (6.0–15.9)
Weight (kg)	40.4 (13.2)	35.9 (15.1)
Duration of anaesthesia (min)	17.8 (5.6)	20.4 (9.0)
Type of surgery		
Bronchoscopy	3	3
Bronchoscopy and gastroscopy	5	6
Gastroscopy	12	11

Table 2 Induction and recovery times (min) for sevoflurane and halothane anaesthesia (median (10–90 percentile range). *P* values indicate difference between age groups (Kruskal–Wallis); **P* < 0.05 compared with sevoflurane in the same age group (Mann–Whitmey *U* test)

	3–11 months	1–5 yr	6–15 yr	*P*
Loss of eyelash reflex				
Sevoflurane	0.8 (0.6–1.2)	0.8 (0.7–1.2)	0.8 (0.5–1.1)	ns
Halothane	1.4 (0.9–1.7)*	1.3 (1.0–1.8)*	1.8 (1.0–2.6)*	< 0.05
End of induction				
Sevoflurane	3.1 (2.4–4.8)	3.8 (2.8–6.0)	4.0 (3.2–6.0)	< 0.05
Halothane	4.1 (2.3–6.1)*	4.6 (3.2–6.6)	5.5 (4.1–6.5)*	< 0.05
Emergence				
Sevoflurane	10.5 (3.8–21.0)	11.0 (5.5–23.7)	12.5 (8.0–25.5)	ns
Halothane	27.0 (8.0–34.5)*	29.4 (13.3–38.5)*	18.5 (10.0–25.3)*	< 0.05
Orientation				
Sevoflurane	—	13.5 (10.0–26.6)	14.0 (9.8–27.0)	ns
Halothane	—	33.8 (18.3–43.7)*	21.5 (12.0–31.8)*	< 0.05
Discharge				
Sevoflurane	34.0 (22.0–50.0)	32.0 (22.8–42.5)	32.8 (25.5–53.5)	ns
Halothane	48.5 (33.0–55.8)*	47.0 (35.5–73.0)*	64.5 (42.5–83.0)*	< 0.05

Table 3 Side effects (number of patients and number of separate episodes) during sevoflurane or halothane anaesthesia. VES = Ventricular premature beats. *P* refers to Fisher's exact test

	Sevoflurane	Halothane	*P*
Total number of patients	4	15	0.0044
Number of separate episodes	4	18	0.0007
Arryhthmia	4	14	0.0078
Nodal rhythm	4	9	0.0823
Bigeminy or VES	0	5	0.0287
Laryngeal spasm	0	4	0.0594

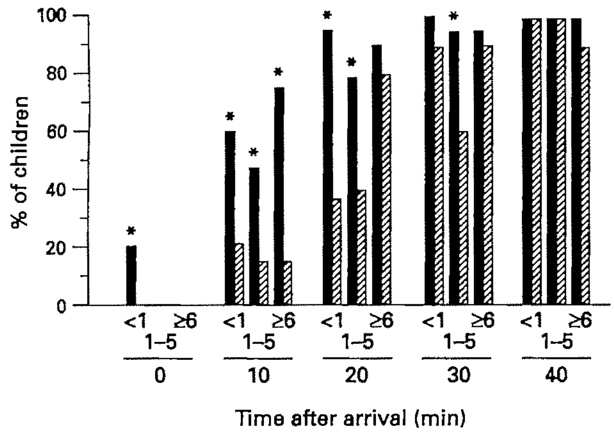


Figure 1 Percentage of children with modified Aldrete scores ≥ 8 at 10-min intervals after arrival in the post-anaesthetic care unit. ■ = sevoflurane and ▨ = halothane groups for the three different age groups (< 1 yr, 1–5 yr and ≥ 6 yr).
* Significantly different from halothane patients of the same age.

anaesthesia, whereas during halothane anaesthesia older children had an earlier recovery (emergence time and time to orientation) than younger patients (table 2). Modified Aldrete scores were significantly greater for sevoflurane than for halothane in several age groups up to 30 min after arrival in the post-anaesthetic recovery unit (fig. 1). Patients anaesthetized with sevoflurane did not express age-related differences in Aldrete scores, but in children anaesthetized with halothane, those aged 1–5 yr old had the slowest normalization of these scores ($P < 0.05$).

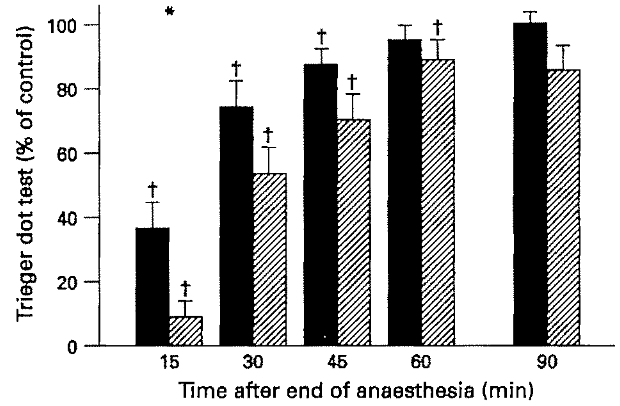


Figure 2 Trieger dot test results (mean, SEM) after sevoflurane (■) and halothane (▨) anaesthesia as a percentage of the pre-anaesthesia control performance in children aged 6–15 yr. * Between-group differences; † Significantly different from pre-anaesthesia performance.

Children in the sevoflurane group had significantly better results for the Trieger dot test at 15 min after anaesthesia than children in the halothane group, and at 60 min they expressed control performance while children in the halothane group failed to do this (fig. 2). Patients were ready to be discharged from the post-anaesthetic recovery unit sooner after the end of sevoflurane anaesthesia than after the end of halothane anaesthesia (table 2). Children of 6–15 yr old who received halothane remained longest in the post-anaesthetic recovery unit because of their slow final recovery from anaesthesia.

At 24-h follow-up, one child in the sevoflurane group had experienced nausea and vomiting, compared with six children in the halothane group ($P < 0.05$). No infant had nausea or vomiting. Children's own appreciation of the quality of induction of the inhalation anaesthesia was assessed in children older than 2 yr. Induction was rated significantly better after sevoflurane than after halothane anaesthesia (table 4). Children's or their parents' willingness to receive further anaesthesias by a similar method was significantly greater after sevoflurane than after halothane anaesthesia (table 4).

Table 4 Patients' or parental experience of anaesthesia (number of patients (percentage of patients). *P* refers to Fisher's exact test

	Sevoflurane ($n = 60$)	Halothane ($n = 60$)	*P*
Type of induction			0.0001
Pleasant	27/35 (77%)	9/34 (26%)	
Unpleasant	4.35 (11%)	17/34 (50%)	
Indifferent	4/35 (11%)	8/34 (24%)	
Similar anaesthetic again			0.0001
Yes	50/59 (85%)	26/60 (43%)	
No	0/59 (0%)	4/60 (7%)	
Maybe	9/59 (15%)	30/60 (50%)	

Discussion

This study highlighted several important findings. First, pure inhalation anaesthesia for procedures that do not require premedication or postoperative analgesia was rated significantly better by children or their parents when the volatile agent used was sevoflurane rather than halothane. Second, sevoflurane, even at relatively high concentrations, produced significantly less side effects than halothane. Third, children were anaesthetized more rapidly and recovery and discharge from the anaesthetic recovery area occurred earlier if sevoflurane rather than halothane was used.

Our induction technique simulated a vital capacity rapid inhalation induction [13] even though young children or infants were unable to take a deep breath and exhalation before application of a face mask. However, a concentration of 7% sevoflurane or 3% halothane in nitrous oxide and oxygen provided much greater speed of induction of anaesthesia than techniques of sevoflurane anaesthesia published previously [5–9]. One MAC of sevoflurane is 2.5–3.2% and that of halothane 0.8–1.2% in these age groups [10, 11]. As nitrous oxide potentiates halothane more than sevoflurane [11], we estimate that our inspired anaesthetic doses were slightly greater in the halothane than in the sevoflurane group (3.5 *vs* 3.0 MAC equivalents). However, because induction times were shorter in the sevoflurane group and time to loss of eyelash reflex was less than 1 min in these patients, we believe that effective brain concentrations occurred much earlier in the sevoflurane than in the halothane group. Two factors promoted this: low solubility of sevoflurane [11] and minimal airway irritation produced by sevoflurane compared with halothane [14].

We regard our results on children's or their parents' experience on the quality of anaesthesia as very important. Children are seldom asked for their own preference for any particular anaesthetic drug. Our results clearly indicate that sevoflurane is accepted more readily than halothane, even though halothane has been the traditional inhalation agent for children. Pleasant smell may be one of the factors favouring sevoflurane. Other valuable characteristics of sevoflurane anaesthesia include round and smooth induction, good physiological and psychomotor recovery, and a low incidence of side effects. Our anaesthetic method used a single volatile agent. Anticholinergic agents were not given as cardiac arrhythmias during bronchoscopy have been reported to be less frequent after placebo than after either atropine or glycopyrronium [15]. As premedication and opioids were also avoided, children did not have the drowsiness or nausea associated with these agents. Thus the children's experience of anaesthesia was related mainly to the particular volatile agent used.

We did not expect to find such a difference in the incidence of clinically significant side effects between the two anaesthetic groups. The most frequent side effect was cardiac arrhythmia and five episodes of bigeminy or ventricular premature beats required i.v. lignocaine for treatment. All cases occurred in patients receiving halothane. This result corroborates that of Johannesson, Florén and Lindahl [8] who reported that sevoflurane produced less cardiac arrhythmias than halothane during paediatric ENT surgery. However, these investigators used atropine for premedication, and this may have affected their results. We also found that the incidence of postoperative nausea and vomiting was less in the sevoflurane than in the halothane group (one of 40 sevoflurane patients compared with six of 40 halothane patients). Sevoflurane anaesthesia produced remarkably little nausea and vomiting; further studies are indicated to determine if sevoflurane has antiemetic properties.

Acknowledgement

We thank Dr George Meakin, Royal Manchester Children's Hospital, Manchester, for his constructive criticism of this manuscript.

References

1. Woods AM. Pediatric bronchoscopy, bronchography, and laryngoscopy. In: Berry FA, ed. *Anesthetic Management of Difficult and Routine Pediatric Patients*. New York: Churchill Livingstone, 1986; 189–250.
2. Motoyama E. Anesthesia for ear, nose, and throat surgery. In: Motoyama EK, Davis PJ, eds. *Smith's Anesthesia for Infants and Children*. St Louis: CV Mosby Company, 1990; 649–674.
3. Brown TCK, Fisk GC. Anaesthesia for ear, nose and throat operations. In: Brown TCK, Fisk GC, eds. *Anaesthesia for Children*. London: Blackwell Scientific Publications, 1992; 228–241.
4. Ferrari LR, Vassalo SA. Anesthesia for otorhinolaryngology. In: Coté CJ, Ryan JF, Todres ID, Goudsouzian NG, eds. *A Practice of Anesthesia for Infants and Children*. Philadelphia: WB Saunders Company, 1993; 311–322.
5. Naito Y, Tamai S, Shingu K, Fujimori R, Mori K. Comparison between sevoflurane and halothane for paediatric ambulatory anaesthesia. *British Journal of Anaesthesia* 1991; 67: 387–389.
6. Taivainen T, Tiainen P, Meretoja OA, Räihä L, Rosenberg PH. Comparison of the effects of sevoflurane and halothane on the quality of anaesthesia and serum glutathione transferase alpha and fluoride in paediatric patients. *British Journal of Anaesthesia* 1994; 73: 590–595.
7. Piat V, Dubois MC, Johanet S, Murat I. Induction and recovery characteristics and hemodynamic responses to sevoflurane and halothane in children. *Anesthesia and Analgesia* 1994; 79: 840–844.
8. Johannesson GP, Florén M, Lindahl SGE. Sevoflurane for ENT-surgery in children. A comparison with halothane. *Acta Anaesthesiologica Scandinavica* 1995; 39: 546–550.
9. Sarner JB, Levine M, Davis PJ, Lerman J, Cook DR,

Motoyama E. Clinical characteristics of sevoflurane in children. A comparison with halothane. *Anesthesiology* 1995; **82**: 38–46.

10. Gregory GA, Eger EI II, Munson ES. The relationship between age and halothane requirements in man. *Anesthesiology* 1969; **30**: 488–491.
11. Lerman J, Sikich N, Kleinman S, Yentis S. The pharmacology of sevoflurane in infants and children. *Anesthesiology* 1994; **80**: 814–824.
12. Aldrete JA, Kroulik D. A postanesthetic recovery score. *Anesthesia and Analgesia* 1970; **49**: 924–934.
13. Yurino M, Kimura H. Induction of anesthesia with sevoflurane, nitrous oxide, and oxygen: a comparison of spontaneous ventilation and vital capacity rapid inhalation induction (VCRII) techniques. *Anesthesia and Analgesia* 1993; **76**: 598–601.
14. Doi M, Ikeda K. Airway irritation produced by volatile anaesthetics during brief inhalation: comparison of halothane, enflurane, isoflurane and sevoflurane. *Canadian Journal of Anaesthesia* 1993; **40**: 122–126.
15. Grønnebech H, Johansson G, Smedebøl M, Valentin N. Glycopyrrolate vs. atropine during anaesthesia for laryngoscopy and bronchoscopy. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 454–457.

British Journal of Anaesthesia 1996; **76**: 772–776

Cricoid pressure applied after placement of the laryngeal mask prevents gastric insufflation but inhibits ventilation

T. ASAI, K. BARCLAY, C. MCBETH AND R. S. VAUGHAN

Summary

We studied 50 patients, in a blind, crossover study, to assess if cricoid pressure applied after placement of the laryngeal mask prevented gastric insufflation without affecting ventilation. After induction of anaesthesia and neuromuscular block, a laryngeal mask was inserted and confirmed to be placed correctly. The lungs were ventilated with a maximum inflation pressure of 15 cm H_2O. In the first 25 patients, expiratory volumes were measured with and without cricoid pressure (30 N). On both occasions, a free hand was placed under the patient's neck. In the next 25 patients, the effect of cricoid pressure on ventilation without support of the neck was also studied. The effect of cricoid pressure with support of the neck on gastric insufflation was then assessed using a stethoscope in all 50 patients, while the lungs were ventilated with a maximum inflation pressure of 30 cm H_2O. At the end of the study, the position of the mask was re-assessed. Cricoid pressure significantly decreased mean expiratory volume ($P \ll 0.001$). This inhibitory effect was significantly greater when the pressure was applied without support of the neck ($P \ll 0.001$). Cricoid pressure significantly reduced the incidence of gastric insufflation (12 patients *vs* one patient; $P \ll 0.001$; 95% CI for difference 10.5–33.5%). In no patient was the mask dislodged after these procedures. Thus, although cricoid pressure applied after insertion of the laryngeal mask prevented gastric insufflation, it also decreased ventilation. The inhibitory effect of cricoid pressure on ventilation without support of the neck was greater than cricoid pressure with support of the neck. (*Br. J. Anaesth.* 1996; **76**: 772–776)

Key words
Equipment, masks anaesthesia. Larynx, cricoid pressure.

The laryngeal mask has a potential role in patients with difficult airways. It has been used successfully to facilitate ventilation in patients in whom ventilation via a face mask, or tracheal intubation, or both, had failed [1, 2]. However, it cannot reliably prevent gastric insufflation, regurgitation or pulmonary aspiration [3, 4]. Cricoid pressure is thus necessary in patients with increased risk of pulmonary aspiration.

Cricoid pressure, when applied *before* insertion, impedes the correct positioning of the laryngeal mask and may prevent adequate ventilation [5–7]. Thus, it has been suggested that cricoid pressure should be released temporarily during insertion of the laryngeal mask and, when the mask has been inserted, cricoid pressure should be reapplied [5, 7].

Cricoid pressure applied *after* placement of the laryngeal mask effectively prevents regurgitation [8]. However, it is not known if cricoid pressure applied after placement of the laryngeal mask prevents gastric insufflation and if it affects ventilation through the mask. Therefore, in this study we examined if cricoid pressure applied after placement of the laryngeal mask effectively prevented gastric insufflation without inhibiting ventilation. It has been reported that there are differences in the various effects of cricoid pressure with and without support of the neck [7, 9]. We also studied if there was a difference in the effect on ventilation between these two methods of cricoid pressure.

Patients and methods

After obtaining approval from the local Research Ethics Committee and written informed consent, we studied 50 female patients, ASA I or II, aged 18–65 yr, undergoing elective surgery, in whom neuromuscular block was indicated. Patients were excluded if they had any pathology of the neck, upper respiratory or upper alimentary tracts, or were at risk of pulmonary aspiration of gastric contents. Patients with Mallampati class 3 [10] or class 4 [11] were also excluded.

Temazepam 20 mg was given orally as premedication. In the anaesthetic room, an electrocardiograph, pulse oximeter and arterial pressure cuff were attached. After preoxygenation, anaesthesia was induced with either thiopentone or propofol i.v. and neuromuscular block was produced with vecuronium. Neuromuscular block was confirmed with a peripheral nerve stimulator. Anaesthesia was maintained with either enflurane or isoflurane in oxygen during the study.

After neuromuscular block was achieved, pillows were replaced by a firm pad (6 cm in height). The pad was placed under the patient's occiput, but not under the neck. A size 3 or size 4 laryngeal mask was inserted using the method described in the manu-

---

TAKASHI ASAI, MD, KEITH BARCLAY, MB, CHB, FRCA, CHRISTINE MCBETH, FRCA, RALPH S. VAUGHAN, MB, BS, FRCA, Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XW. Accepted for publication: January 29, 1996.

facturer's instruction manual [12]. The cuff of the mask was inflated with the recommended maximum volume of air (20 and 30 ml, respectively). The breathing system was connected to the laryngeal mask.

ROUTINE ASSESSMENT OF VENTILATION VIA THE LARYNGEAL MASK

The adequacy of ventilation was assessed by manual ventilation. Ventilation was judged as adequate when the chest expanded with inflation with a satisfactory compliance. If it was not possible to ventilate the lungs adequately, one more attempt at placement of the laryngeal mask was allowed. If unsuccessful, the patient was withdrawn from the study. Any apparent airleak from the gap between the mask and pharynx was noted.

After successful insertion, a bite-block (a wad of gauze) was inserted and both the laryngeal mask and the bite-block were fixed to the patient's face with tape. The lungs were subsequently inflated using the ventilator (Siemens Servo-C) with a setting of square waveform in the pressure control mode. An inspiratory–expiratory ratio of 1:3 was used and the pressure was initially set to 15 cm H_2O.

ASSESSMENT OF INITIAL POSITION OF THE LARYNGEAL MASK

The position of the laryngeal mask was assessed using a fibreoptic bronchoscope, as described previously [7]. The mask was arbitrarily considered to be placed correctly when all of the following criteria were fulfilled: (1) the skin overlying both the thyroid and cricoid cartilages bulged mildly during inflation of the cuff; (2) neither the mask nor the tube was twisted; (3) the glottis was seen through the fibrescope; and (4) neither the tip of the mask nor the oesophagus was seen through the fibrescope [13].

EFFECT OF CRICOID PRESSURE ON VENTILATION VOLUME

In a random, crossover design, we assessed the adequacy of ventilation with and without cricoid pressure. In the first 25 patients, we studied the effect of cricoid pressure which was applied with a free hand placed under the patient's neck (i.e. bimanual cricoid pressure). On one occasion, cricoid pressure was applied with a cricoid yoke [7], at a force of 30 N [14]; on the other occasion, the yoke was placed on the cricoid cartilage, but pressure was not applied (sham pressure). The order of the test pressures was randomized by tossing a coin.

The investigator assessing ventilation volumes and the presence of gastric insufflation (see below) was blind to the application of cricoid pressure by placing a screen between the patient and the investigator. The other investigator, who applied a test pressure on cricoid cartilage, was also blind as to the volumes of ventilation and the presence of gastric insufflation. Expiratory volumes, as a reflection of ventilation volumes, were recorded from the sixth to the 10th breaths and mean values were calculated.

We found that cricoid pressure inhibited ventilation through the laryngeal mask in the first 25 patients (see results). Therefore, we studied another 25 patients to determine if there was a difference in the inhibitory effect on ventilation between two different methods of cricoid pressure. Three different methods were used in this part of the study: sham pressure, cricoid pressure with support of the neck (bimanual method) and cricoid pressure without support of the neck (single-handed method). These three test pressures were applied in turn. The order was randomized by choosing a card without replacement from three cards indicating the three test pressures. Expiratory volumes were recorded from the sixth to the 10th breaths for each circumstance.

EFFECT OF CRICOID PRESSURE ON GASTRIC INSUFFLATION

After assessment of the effect of cricoid pressure on ventilation through the laryngeal mask, we studied the effect of cricoid pressure on gastric insufflation in all 50 patients. The inflation pressure was increased from 15 to 30 cm H_2O. On one occasion, cricoid pressure was applied bimanually and on the other occasion, no pressure was applied. On each of the two occasions, the presence of gastric insufflation was assessed by auscultation over the epigastrium. The lungs were inflated for a maximum of five times for each situation. Lawes, Campbell and Mercer [15] have shown that a volume of gas, as little as 5 ml, entering the stomach from the oesophagus can be detected. We also confirmed that "bubbling" sounds were detected reliably by a stethoscope placed over the epigastrium during insufflation of 5 ml of air through a nasogastric tube into the stomach. Any apparent air leak from the gap between the laryngeal mask and the pharynx was also noted.

ASSESSMENT OF FINAL POSITION OF THE LARYNGEAL MASK

At the end of the procedure, the position of the laryngeal mask was re-assessed using a fibreoptic bronchoscope to examine if the mask had been dislodged by application of cricoid pressure and ventilation with an inflation pressure of 30 cm H_2O.

MEASUREMENTS AND STATISTICAL ANALYSIS

Ventilation volumes and the presence of gastric insufflation were recorded. The mean expired tidal volume between the sixth and 10th breath was calculated. Normal plots (plots of normal scores) showed that the data for the differences in expiratory volumes between the different test pressures were not normally distributed. The non-parametric Wilcoxon signed rank sum test was therefore used to compare mean expiratory volumes in patients in whom only bimanual and sham pressures were used. In patients in whom all three test pressures were used, Friedman's non-parametric two-way analysis of variance was used to compare mean expiratory volumes. If this proved significant, the Wilcoxon signed rank sum test was used to compare ventilation between single and bimanual cricoid pressure. Fisher's exact test was used to compare the incidence of gastric insufflation with and without cricoid pressure. $P < 0.05$ was considered significant. Confidence intervals (CI) for the difference in mean expiratory volume and the incidence of gastric insufflation with and without test pressure were also calculated.

A previous study has shown that without cricoid pressure, the incidence of gastric insufflation is about 30 % when the lungs are ventilated via the laryngeal mask with a maximum inflation pressure of 30 cm H_2O [3]. We considered that cricoid pressure would be effective if the incidence was decreased to less than 5 %. To detect this reduction, with a power of 85 %, 50 patients were required for $P = 0.05$ [16].

We studied 50 females, aged 22–67 yr, weight 51–86 kg, and with Mallampati class 1 and 2 (37 and 13 patients, respectively).

Results

ROUTINE ASSESSMENT OF VENTILATION VIA THE LARYNGEAL MASK

The laryngeal mask was placed easily at the first attempt and ventilation was considered adequate in all patients who were included in the study. In one other patient, however, placement of the mask failed after two attempts and thus this patient was withdrawn from the study. A size 4 mask was used in 44 and a size 3 in the remaining six patients. There was no detectable air leak from the gap between the laryngeal mask and the pharynx in any patient when the lungs were ventilated with a maximum inflation pressure of 15 cm H_2O.

ASSESSMENT OF INITIAL POSITION OF THE LARYNGEAL MASK

During inflation of the mask, the tissue overlying both the thyroid and cricoid cartilages bulged. The glottis was always seen directly below the grille of the laryngeal mask when the position of the mask was assessed using a fibreoptic bronchoscope. Neither the mask nor the tube was twisted; neither the tip of the mask nor the oesophagus was seen in any patient. Therefore, the position of the mask was judged as correct in all patients.

EFFECT OF CRICOID PRESSURE ON VENTILATION VOLUME

In the first 25 patients, median expiratory volume was 733 (range 438–1413) ml when no pressure was applied to the cricoid cartilage. Bimanual cricoid pressure decreased the expiratory volume to 501 (169–1133) ml, and this inhibitory effect was significant ($P \ll 0.001$) (95 % CI for difference 93–223 ml) (fig. 1).

In the second 25 patients, in whom the effects of both single-handed and bimanual cricoid pressures were studied, Friedman's two-way analysis of variance showed that mean expiratory volume was significantly different between the three test pressures ($P \ll 0.001$). The inhibitory effect of single-handed cricoid pressure was significantly greater than that of bimanual cricoid pressure ($P \ll 0.001$) (95 % CI for difference 88–290 ml) (fig. 1).

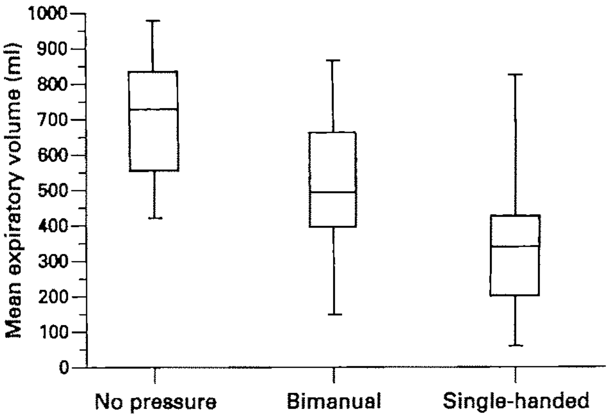


Figure 1 Box-and-whisker plots of the data for mean expiratory volume (calculated from the sixth to the 10th breaths) when either no, bimanual or single-handed cricoid pressure was applied. The box indicates the lower and upper quartiles and the central line is the median. The bars at the end of the "whiskers" are 2.5 % and 97.5 % values. The data for no pressure and bimanual cricoid pressure are for 50 patients, whereas those for single-handed cricoid pressure are for the last 25 patients.

EFFECT OF CRICOID PRESSURE ON GASTRIC INSUFFLATION

When inflation pressure was increased from 15 to 30 cm H_2O, gastric insufflation was detected in 12 of 50 patients (24 %) when no pressure was applied on the cricoid cartilage. In contrast, when bimanual cricoid pressure was applied, insufflation occurred in only one of 50 patients (2 %); it occurred under both circumstances in this patient. Bimanual cricoid pressure thus decreased the incidence of gastric insufflation by 22 % ($P \ll 0.001$) (95 % CI 10.5–33.5 %).

At a maximum inflation pressure of 30 cm H_2O, air leaked from a gap between the laryngeal mask and the pharynx in 23 patients (46 %) when no (sham) pressure was applied and in 26 patients (52 %) when bimanual cricoid pressure was applied.

ASSESSMENT OF FINAL POSITION OF THE LARYNGEAL MASK

At the end of the procedure, the position of the laryngeal mask was re-assessed. The position had not changed in any patient.

Discussion

EFFECT OF CRICOID PRESSURE ON VENTILATION

Cricoid pressure significantly decreased ventilation volumes through the laryngeal mask. The cumulative frequency of the expiratory volume per unit body weight (fig. 2) showed that the proportion of patients at a certain expiratory volume was always greater when cricoid pressure was applied compared with sham pressure. In addition, the proportion was also always greater when single-handed cricoid pressure was applied compared with bimanual cricoid pres-

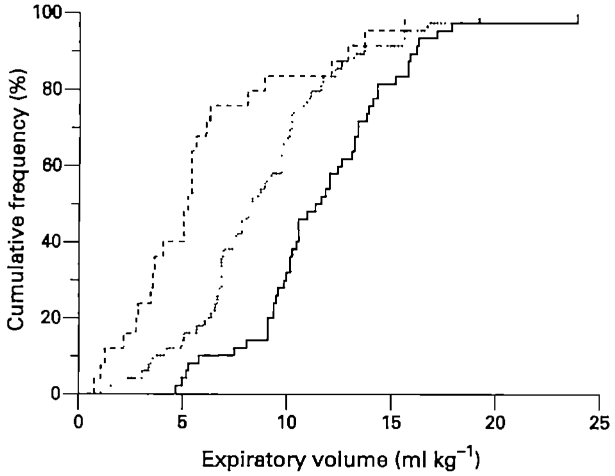


Figure 2 Cumulative frequency of mean expiratory volume (calculated from the sixth to the 10th breaths) when either no (—), bimanual (· · · ·) or single-handed (———) cricoid pressure was applied. The data for no pressure and bimanual cricoid pressure are for 50 patients, whereas those for single-handed cricoid pressure are for the last 25 patients.

sure (fig. 2). These results indicate that ventilation is more likely to be inadequate when cricoid pressure is applied and, in particular, when it is applied without support of the neck (single-handed cricoid pressure). For example, if we arbitrarily consider that ventilation was adequate when the expiratory volume was greater than 8 ml kg^{-1}, ventilation was adequate in most patients when no pressure was applied. In contrast, it was adequate in about 50 % of patients when bimanual cricoid pressure was applied and in only 14 % of patients when single-handed cricoid pressure was applied.

Several differences in the various effects of cricoid pressure with and without support of the neck have been reported [7, 9]. Cricoid pressure without support of the neck tends to flex the head on the neck. In contrast, support of the neck minimizes such flexion [9]. It has been claimed that flexion of the head on the neck may make both ventilation through the face mask and tracheal intubation more difficult [7, 9]. In addition, single-handed cricoid pressure prevents placement of, and ventilation through, the laryngeal mask more often than bimanual cricoid pressure [7]. The findings in this study confirm that support of the neck may reduce the untoward effects associated with cricoid pressure.

We assessed ventilation while the lungs were ventilated by a pressure control mode with a maximum inflation pressure of 15 cm H_2O. We used this mode as we considered that in clinical practice, ventilation wold usually be controlled by squeezing the reservoir bag, feeling the compliance of the lungs. We also considered that we would not inflate the lungs with an inflation pressure greater than 15–20 cm H_2O, to minimize air leak around the laryngeal mask. It is, however, not clear if cricoid pressure decreases ventilation volumes when the lungs are ventilated by a volume-controlled mode.

We used a firm pad to standardize the position of the patient's head and neck. Soft pillows are usually used to support the head and neck during induction of anaesthesia in the UK. This support of the neck by pillows may lessen the inhibitory effect of single-handed cricoid pressure on ventilation.

It has been recommended that cricoid pressure should be released temporarily during placement of the laryngeal mask and that it is re-applied immediately after placement of the mask [5, 7, 13]. From the results of this study we recommend that the patient's neck should be supported when cricoid pressure is applied after placement of the laryngeal mask to minimize the decrease in ventilation through the laryngeal mask.

GASTRIC INSUFFLATION

Cricoid pressure significantly decreases the degree of gastric insufflation while the lungs are ventilated via a face mask in both adults [15, 17, 18] and children [19–21]. We found that cricoid pressure was effective in preventing gastric insufflation even when the laryngeal mask was in place.

When the lungs were ventilated at a maximum inflation pressure of 30 cm H_2O (without cricoid pressure), gastric insufflation occurred in 24 % of patients, whereas air leaked from the gap between the mask and the pharynx in 46 % of patients. In a previous study, where a similar method of ventilation was used, the incidences of gastric insufflation and air leak were 35.4 % and 96 %, respectively, when the lungs were ventilated with an inflation pressure of 30 cm H_2O [3].

One possible reason for these differences between this and previous studies [3] is the difference in the size of the laryngeal mask. In the previous study, a size 3 laryngeal mask was used in females and a size 4 in males [3], whereas in this study, we used a size 4 in most female patients. Thus the incidence of both gastric insufflation and air leak might have been lower in this study because of a "better fit" mask. Brain states that a size 4 mask should be used in adults (both males and females) of average size, and a size 3 mask in small adults [12], although there is no study to confirm this recommendation. Our study may support the claim that the use of the size 4 mask is better than the size 3 mask in females of average size.

The incidence of apparent air leak from a gap between the laryngeal mask and the pharynx was greater than that of gastric insufflation. This finding is consistent with previous results [3]. The higher incidence of air leak around the laryngeal mask may indicate that the mask acts as a pressure-limiting ("pop-off") valve and reduces both the incidence and degree of gastric insufflation. When a face mask is used, gastric insufflation usually occurs at about 30 cm H_2O [15, 17, 21]. Thus the incidence of gastric insufflation is lower when the laryngeal mask is used compared with a face mask.

CRICOID PRESSURE DURING CARDIOPULMONARY RESUSCITATION

The laryngeal mask may be useful as an initial method of airway management during resuscitation until a person competent in tracheal intubation is available [22]. Although application of cricoid pressure during cardiopulmonary resuscitation has been advocated, it is not performed widely [23]. It is recommended that the airway should be maintained by two people when a face mask is used, one holding the mask and the patient's jaw and the other ventilating the lungs [24, 25]. Thus a third person may be required to apply cricoid pressure, which might be impractical. When the laryngeal mask is used, it may be practical to apply cricoid pressure, as one person can maintain both a patent airway and adequate ventilation and the second person can apply cricoid pressure.

In this study, although cricoid pressure decreased the incidence of gastric insufflation, it also inhibited ventilation through the laryngeal mask. It has been claimed from results of a multi-hospital study that the incidence of both gastric insufflation and regurgitation during cardiopulmonary resuscitation may be lower when the laryngeal mask is used compared with a face mask, even when cricoid pressure is *not* applied [22]. It is not clear if cricoid pressure would improve clinical outcome when the laryngeal mask is used during cardiopulmonary resuscitation.

POSITION OF THE LARYNGEAL MASK

The position of the laryngeal mask had not changed in any patient at the end of the experimental procedures. Thus application of cricoid pressure and ventilation of the lungs with an inflation pressure of 30 cm H_2O for a short duration after placement of the laryngeal mask did not usually dislodge the mask, when the mask was placed and fixed correctly to the patient's face. This finding is consistent with a previous observation [26]. However, it is not certain if cricoid pressure or ventilation with a high inflation pressure for a long duration would dislodge the mask. Dislodgement could be more likely to occur if the mask is not placed or fixed correctly. There is, however, no evidence to support these possibilities.

In summary, we have shown that although cricoid pressure applied after correct placement of the laryngeal mask significantly decreases the incidence of gastric insufflation, it also decreases the adequacy of ventilation. We also have shown that the inhibitory effect on ventilation by cricoid pressure without supporting the neck is greater than cricoid pressure with support of the neck. The patient's neck should thus be supported when cricoid pressure is applied after successful placement of the laryngeal mask.

Acknowledgement

We thank Professor Emeritus W. W. Mapleson, University of Wales College of Medicine, for advice on statistical analysis.

References

1. Calder I, Ordman AJ, Jackowski A, Crockard HA. The Brain laryngeal mask airway. An alternative to emergency tracheal intubation. *Anaesthesia* 1990; **45**: 137–139.
2. McClune S, Regan M, Moore J. Laryngeal mask airway for Caesarean section. *Anaesthesia* 1990; **45**: 227–228.
3. Devitt JH, Wenstone R, Noel AG, O'Donnell MP. The laryngeal mask airway and positive-pressure ventilation. *Anesthesiology* 1994; **80**: 550–555.
4. Nandi M, Maltby JR. Vomiting and aspiration pneumonitis with the laryngeal mask airway. *Canadian Journal of Anaesthesia* 1992; **39**: 69–70.
5. Ansermino JM, Blogg CE. Cricoid pressure may prevent insertion of the laryngeal mask airway. *British Journal of Anaesthesia* 1992; **69**: 465–467.
6. Asai T, Barclay K, Power I, Vaughan RS. Cricoid pressure impedes placement of the laryngeal mask airway and subsequent tracheal intubation through the mask. *British Journal of Anaesthesia* 1994; **72**: 47–51.
7. Asai T, Barclay K, Power I, Vaughan RS. Cricoid pressure impedes placement of the laryngeal mask airway. *British Journal of Anaesthesia* 1995; **74**: 521–525.
8. Strang TI. Does the laryngeal mask airway compromise cricoid pressure? *Anaesthesia* 1992; **47**: 829–831.
9. Selwyn Crawford J. The "contracricoid' cuboid aid to tracheal intubation. *Anaesthesia* 1982; **37**: 345.
10. Mallampati SR, Gatt SP, Gugino LD, Desai SP, Waraksa B, Freiberger D, Liu PL. A clinical sign to predict difficult tracheal intubation: a prospective study. *Canadian Anaesthetists Society Journal* 1985; **32**: 429–434.
11. Samsoon GLT, Young JRB. Difficult tracheal intubation: a retrospective study. *Anaesthesia* 1987; **42**: 487–490.
12. Brain AIJ. *The Intavent Laryngeal Mask. Instruction Manual*, 2nd Edn, 1993.
13. Asai T, Morris S. The laryngeal mask airway: its features, effects and role. *Canadian Journal of Anaesthesia* 1994; **41**: 930–960.
14. Vanner RG, Pryle BJ. Regurgitation and oesophageal rupture with cricoid pressure: a cadaver study. *Anaesthesia* 1992; **47**: 732–735.
15. Lawes EG, Campbell I, Mercer D. Inflation pressure, gastric insufflation and rapid sequence induction. *British Journal of Anaesthesia* 1987; **59**: 315–318.
16. Miller DK, Homan SM. Graphical aid for determining power of clinical trials involving two groups. *British Medical Journal* 1988; **297**: 672–676.
17. Ruben H, Knudsen EJ, Carugati G. Gastric inflation in relation to airway pressure. *Acta Anaesthesiologica Scandinavica* 1961; **5**: 107–114.
18. Petito SP, Russell WJ. The prevention of gastric insufflation—a neglected benefit of cricoid pressure. *Anaesthesia and Intensive Care* 1988; **16**: 139–143.
19. Salem MR, Wong AY, Mani M, Sellick BA. Efficacy of cricoid pressure in preventing gastric insufflation during bag-mask ventilation in pediatric patients. *Anesthesiology* 1974; **40**: 96–98.
20. Admani M, Yeh TF, Jain R, Mora A, Pildes RS. Prevention of gastric insufflation during mask ventilation in newborn infants. *Critical Care Medicine* 1985; **13**: 592–593.
21. Moynihan RJ, Brock-Utne JG, Archer JH, Feld LH, Kreitzman TR. The effect of cricoid pressure on preventing gastric insufflation in infants and children. *Anesthesiology* 1993; **78**: 652–656.
22. Results of a multicentre trial. The use of the laryngeal mask airway by nurses during cardiopulmonary resuscitation. *Anaesthesia* 1994; **49**: 3–7.
23. Melker RJ. Recommendations for ventilation during cardiopulmonary resuscitation: time for change? *Critical Care Medicine* 1985; **13**: 882–883.
24. Baskett PJF. Advances in cardiopulmonary resuscitation. *British Journal of Anaesthesia* 1992; **69**: 182–193.
25. Emergency Cardiac Care Committee and Subcomittees. American Heart Association. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Part III: Adult advanced cardiac life support. *Journal of the American Medical Association* 1992; **268**: 2199–2241.
26. Asai T. The laryngeal mask airway as an aid to intubation in patients at increased risk of aspiration? *Anesthesiology* 1993; **78**: 1197.

British Journal of Anaesthesia 1996; **76**: 777–779

Effects of surgical skin incision on respiration in patients anaesthetized with enflurane†

R. W. SUTHERLAND AND G. B. DRUMMOND

Summary

We measured ventilation in 12 subjects anaesthetized with enflurane (end-tidal concentration 1.25–1.45%) and nitrous oxide to assess the effect of surgical stimulation on ventilation in humans. Tidal volume and respiratory timing were measured by pneumotachograph before and just after a standardized surgical skin incision. Surgical stimulation increased ventilation by increasing tidal volume, which increased progressively over the first five breaths after incision. The first breath after the stimulus was prolonged, but the timing of the subsequent breaths returned rapidly to the duration observed before incision. Ventilation increased from median 3.6 (quartiles 2.9, 4.3) to 5.4 (3.8, 7.0) litre min^{-1} ($P < 0.01$). The increased tidal volume was not associated consistently with shortening of inspiratory duration. (*Br. J. Anaesth.* 1996; **76**: 777–779)

Key words

Anaesthetics volatile, enflurane. Ventilation, effects. Ventilation, pattern. Surgery, ventilatory response.

Traditional teaching is that depth of anaesthesia can be assessed by a variety of clinical signs [1]. Anaesthesia affects tidal volume and frequency of ventilation, and these variables are commonly used in clinical practice to assess depth of anaesthesia, although ventilatory frequency is influenced more by the volatile anaesthetic agent used than by depth of anaesthesia [2].

Spontaneous ventilation during surgery is influenced by both anaesthetic and stimulus. During anaesthesia with halothane or isoflurane, surgical skin incision is followed by an increase in the depth and rate of breathing [3, 4]. Stimuli in experimental animals cause similar increases in ventilation [5]. An increase in tidal volume, associated with a decrease in the duration of the respiratory cycle, suggests that respiration could be controlled in a manner proposed by Clark and von Euler [6]. The aim of this study was to demonstrate more exactly the pattern of response of respiration in anaesthetized patients after surgical skin incision, and to use this response to investigate the relationship between tidal volume and timing of the respiratory cycle.

Patients and methods

After obtaining local Ethics Committee approval and written informed consent, we studied 12 patients (eight female), ASA I or II, undergoing elective surgery for varicose veins. Patients were aged 30–63 yr and weighed 45–85 kg. No premedication was given. With the patient supine, anaesthesia was induced with propofol 2.5 mg kg^{-1} i.v., a laryngeal mask airway was inserted and anaesthesia maintained with enflurane and 66% nitrous oxide in oxygen. End-tidal enflurane concentrations were measured by sidestream sampling from a connector attached to the laryngeal mask airway using a Hewlett-Packard M1025 gas analyser, calibrated according to the manufacturer's instructions. The inspired enflurane concentration was adjusted to obtain a stable end-tidal value, within 0.1% for each patient, at 1.25–1.45%. Patients breathed spontaneously via a screen pneumotachograph (Mercury F100L) from a circle anaesthesia system. The pneumotachograph was calibrated on each occasion with a standard air syringe. The pneumotachograph output was digitized using a laptop computer fitted with an analogue-to-digital converter and recorded with Cardas software (version 6.1) (Oxcams, Oxford), which allowed instantaneous display of flow against time.

After surgical skin preparation and draping (skin clips were not used), each patient was allowed to breathe undisturbed for at least 2 min before a skin incision was made over the femoral vein in the groin for exploration of the saphenofemoral junction. The time of the start of incision was recorded onto the computer flow display. No attempt was made to synchronize the incision with the respiratory cycle.

The flow signal was later replayed and integrated using custom-written software to obtain a breath-by-breath volume signal, which was analysed to measure inspiratory duration (T_I), expiratory duration (T_E) and tidal volume (V_T). Instantaneous ventilation was calculated from tidal volume and respiratory cycle duration, and mean inspiratory flow rate was calculated as V_T/T_I.

Comparisons were made of these variables within individual subjects by paired comparison using the median values obtained from 10 breaths before

---

R. W. SUTHERLAND*, FRCA, G. B. DRUMMOND, MA, FRCA, Department of Anaesthetics, Royal Infirmary, Edinburgh EH3 9YW. Accepted for publication: January 16, 1996.

*Present address for correspondence: Department of Anaesthesia, Queens Medical Centre, Nottingham NG7 2UH.

†Presented in part at the Anaesthetic Research Society, London Meeting, November 11–12, 1994 (*British Journal of Anaesthesia* 1995; 74: 497P–498P).

incision for each patient, with the median of 10 breaths after incision in the same patient (Wilcoxon paired test). $P < 0.05$ was considered significant. In addition, the first breath after incision was compared with the median value obtained from 10 breaths before incision, to assess the immediate responses. Individual V_T and T_I values in each subject before and after incision were plotted to assess the changes in breathing pattern. Statistical analysis was with Minitab release 8.2 using MS DOS version 6.2. Results are reported as median (quartile) values.

Results

Immediately before incision, mean end-tidal enflurane concentration was 1.39% (SD 0.06%). No patient showed limb movement on skin incision, but skin incision had an immediate effect on breathing pattern (fig. 1).

TIDAL VOLUME

Before stimulation, median tidal volume was stable with no significant trend in magnitude. Tidal volume of the first breath after stimulation had a greater volume (297, 178–437 ml) than the median of the values of the 10 preceding breaths (195, 151–211 ml). There was then a progressive increase in tidal volume over the next five breaths. Median tidal volumes for the 10 breaths after incision were significantly greater than the tidal volumes for the preceding 10 breaths (271, 225–363 ml compared with 195, 151–211 ml; $P < 0.01$).

MEAN INSPIRATORY FLOW RATE (V_T/T_I)

Surgical stimulation was associated with a small immediate increase in V_T/T_I in the first breath, and a progressive further increase over the next five breaths. The marked increase in tidal volume at the first breath was clearly not the result of an increase in inspiratory flow. The 10 breaths after stimulation had a significantly greater V_T/T_I than the preceding 10 breaths (10.6, 8.6–15.3 litre min^{-1} compared with 7.4, 6.9–9.0 litre min^{-1}; $P < 0.01$).

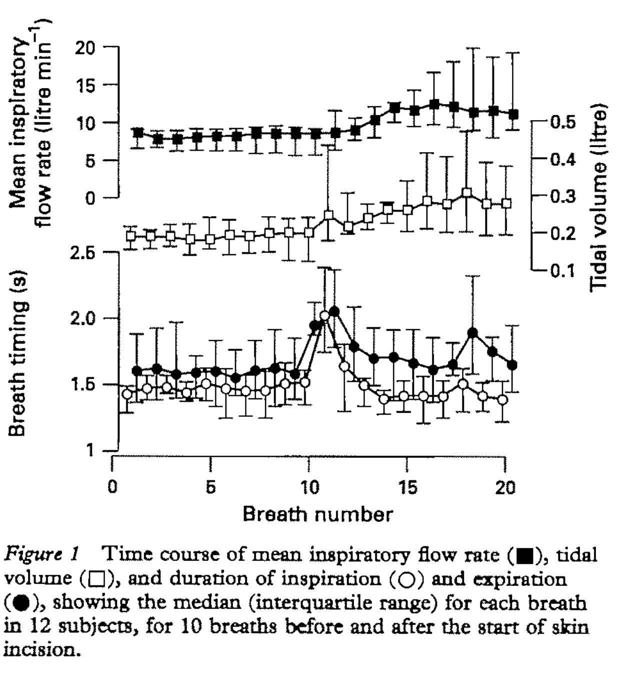


Figure 1 Time course of mean inspiratory flow rate (■), tidal volume (□), and duration of inspiration (○) and expiration (●), showing the median (interquartile range) for each breath in 12 subjects, for 10 breaths before and after the start of skin incision.

RESPIRATORY TIMING

The first breath after stimulation had a longer T_I (1.99, 1.55–2.42 s) and T_E (1.95, 1.63–2.28 s) than the preceding 10 breaths (1.49, 1.35–1.70 s and 1.60, 1.40–1.85 s, respectively) ($P < 0.05$). The timing of the subsequent breaths reverted to that before stimulation.

Minute volume had a pattern similar to mean inspiratory flow rate, and increased progressively for the first five breaths after stimulation. The 10 breaths after stimulation had a significantly greater minute volume (4.9, 3.8–7.0 litre min^{-1} compared with 3.6, 2.9–4.3 litre min^{-1} before stimulation; $P < 0.01$).

RELATIONSHIP BETWEEN V_T AND T_I

There was no clear relationship between V_T and T_I. Stimulation was associated with an increase in V_T in 10 subjects, of whom six showed a reduction in V_T and four an increase. Inspiratory duration decreased significantly in only two patients.

Discussion

Volatile anaesthetics in general, and enflurane in particular, are respiratory depressants [7]. Surgical stimulation can antagonize this depression, but little work has been done to assess the features of the increase in ventilation [3, 4]. Difficulties with standardizing the degree of stimulation have hampered studies of the effects of surgical stimulation on respiration. The intensity of the stimulus depends on the site of surgery and the degree of trauma. We attempted to standardize the stimulus by using a single skin incision in one body site. We also restricted our observations to breaths shortly after stimulation, so that secondary effects caused by changes in ventilation would have only small effects. The laryngeal mask may have caused some stimulation but our experience is that it is well tolerated at even very light levels of anaesthesia, in many instances better than the manipulations associated with conventional mask anaesthesia.

We found that stimulation had an immediate effect on the timing of respiration, followed by reversion to the timing before the stimulus. The speed of this response resembled the rapid responses in respiratory timing to stimuli mediated by nervous afferent activity, such as limb nerve stimulation [8], intercostal nerve stimulation [9], vagal stimuli [10] and peripheral chemoreceptor stimulation [11]. However, it is remarkable how respiratory timing reverts to the previous pattern after one breath. The remainder of the response to surgical stimulation was similar to that seen with a stimulus such as hypercapnia, which has a great influence on tidal volume, and less on respiratory timing [12].

Our findings do not support the possibility that lung volume affects inspiratory duration in these circumstances [2, 6].

Surgical stimulus caused a progressive increase in mean inspiratory flow rate over the first five breaths after the stimulus. Noxious stimuli result in extensive activation of brainstem reticular neurones [13], which can cause an increase in respiratory output, particularly in the rate of increase of inspiratory activity [8]. However, increased reticular system activity causes increases in both tidal volume and frequency [14], whereas in this study only drive increased. This resembles the response to a chemoreceptor stimulus [12].

Studies of other volatile anaesthetic agents with different effects on ventilatory frequency, such as halothane, would be of interest. It might also be that other forms of stimulation, in particular those carried from the viscera by the vagus, may result in different patterns of response, because vagal input in the nucleus tractus solitarius is related closely to respiratory reflex control.

In summary, we found that surgical stimulation during enflurane anaesthesia caused a slow increase in central respiratory drive and minute volume, but only a transient change in respiratory timing. Depth of respiration, or mean inspiratory flow rate, is therefore a useful index of respiratory response to surgical stimulation during anaesthesia with enflurane, but ventilatory frequency not.

Acknowledgement

We thank Dr P. K. Wraith who wrote the program to analyse the flow signal.

References

1. Consultant Committee for Revision of Fundamentals of Anaesthesia. General Anesthesia. In: *Fundamentals of Anesthesia.* Philadelphia: WB Saunders, 1954; 56–129.
2. Drummond GB. Effect of airway occlusion on respiratory timing during anaesthesia with enflurane or halothane. *British Journal of Anaesthesia* 1984; **56**: 215–221.
3. Cullen DJ, Eger EI, Stevens WC, Dolan WM, Miller RD, Way WL. Clinical signs of anesthesia. *Anesthesiology* 1972; **36**: 21–36.
4. Eger EI, Dolan WM, Stevens WC, Miller RD, Way WL. Surgical stimulation antagonizes the respiratory depression produced by Forane. *Anesthesiology* 1972; **36**: 544–549.
5. Hida W, Shindoh C, Kikuchi Y, Chonan T, Inoue H, Sasaki H, Takishima T. Ventilatory response to phasic contraction and passive movement in graded anesthesia. *Journal of Applied Physiology* 1986; **61**: 91–97.
6. Clark FJ, von Euler C. On the regulation of depth and rate of breathing. *Journal of Physiology (London)* 1972; **222**: 267–295.
7. Calverley RK, Smith NT, Jones CW, Prys-Roberts C, Eger EI. Ventilatory and cardiovascular effects of enflurane anesthesia during spontaneous ventilation in man. *Anesthesia and Analgesia* 1978; **57**: 610–618.
8. St John WM. Influence of reticular mechanisms upon hypoglossal trigeminal and phrenic activities. *Respiration Physiology* 1986; **66**: 27–40.
9. Remmers JE, Marttila I. Action of intercostal muscle afferents on the respiratory rhythm of anesthetized cats. *Respiration Physiology* 1975; **24**: 31–41.
10. Millhorn DE, Kiley JP. Effect of graded cooling of intermediate areas on respiratory response to vagal input. *Respiration Physiology* 1984; **58**: 51–64.
11. Lipski J, Trzebski A, Chodobska J, Kruk P. Effects of carotid chemoreceptor excitation on medullary expiratory neurons in cats. *Respiration Physiology* 1984; **57**: 279–291.
12. Knill RL, Manninen PH, Clement JL. Ventilation and chemoreflexes during enflurane sedation and anaesthesia in man. *Canadian Anaesthetists Society Journal* 1979; **26**: 353–360.
13. Casey KL. Somatosensory responses of bulboreticular units in the awake cat. *Science* 1971; **173**: 77–80.
14. Hugelin A, Cohen MI. The reticular activating system and respiratory regulation in the cat. *Annals of the New York Academy of Sciences* 1963; **109**: 586–603.

British Journal of Anaesthesia 1996; **76**: 780–782

Efficiency of a circle system for short surgical cases: comparison of desflurane with isoflurane

D. J. H. LEE, D. L. ROBINSON AND N. SONI

Summary

Patients undergoing short surgical procedures but requiring ventilation of the lungs were allocated randomly to receive either desflurane or isoflurane by circle absorption system, initially at a high fresh gas flow. The inspired and expired concentrations of the volatile agent were measured and the fresh gas flows reduced to low flow (500 ml min^{-1} total when $F_E/F_I = 0.8$), as measured on a multigas analyser. In patients receiving desflurane ($n = 32$), the median time at which flows were reduced was 5 min (interquartile range (IQR) 1 min) while with isoflurane ($n = 32$), the median time was 19 (IQR 12) min. After the reduction in flow, expired concentrations of volatile agent decreased in both groups. In the isoflurane group the concentration continued to decrease during anaesthesia. In the desflurane group the initial decrease was followed by a slow recovery. We conclude that the circle system can be used efficiently for short anaesthetics using desflurane. (*Br. J. Anaesth.* 1996; **76**: 780–782)

Key words

Anaesthetics volatile, desflurane. Anaesthetics volatile, isoflurane. Equipment, breathing systems.

The advantages of circle systems compared with other breathing systems include conservation of gases, volatile agents, heat and moisture, and reduction in pollution [1]. These benefits are largely dependent on the use of low flows of gas. A large proportion of anaesthetics are of short duration and this does not lend itself to the use of low flows as traditionally it has been assumed to take 15–20 min at high flows to allow the achievement of adequate uptake of inhalation agent. Adequate uptake implies not only that an adequate alveolar concentration is achieved but that it is maintained at an acceptable level after flow reduction. While these initially high flows serve to reduce anxieties about nitrogen washout and nitrous oxide uptake, they also preclude efficient and effective use of the circle.

The advent of new agents with lower solubilities should enable more rapid uptake of agent and so potentially enable the flows to be reduced earlier [2]. Lower solubility also implies less ongoing uptake of the agent and so less risk of the alveolar concentrations decreasing progressively at the low flow rates. If the uptake of agent continues to be high, there is a risk that the alveolar concentration of volatile agent will diminish and result in a change in the depth of anaesthesia.

This study was undertaken to determine if an adequate end-expired concentration could be achieved earlier with desflurane than with isoflurane. We also wished to observe the changes in end-expired concentrations of volatile agents after reduction in flows.

Patients and methods

After obtaining approval from the Riverside Medical Ethics Committee, we studied ASA I or II patients, presenting for surgery, who required tracheal intubation and ventilation of the lungs for surgery. Patients were allocated randomly to receive either 8% desflurane or 1.5% isoflurane. These values were chosen as approximating to 1.5 MAC, so that at $F_E/F_I = 0.8$, the values would be 6% and 1.2%, respectively, which were of adequate magnitude to preclude awareness even if the expired concentrations decreased significantly after reduction in fresh gas flow. No premedication was given as these were short anaesthetics expected to last 20–30 min. Anaesthesia was induced in the anaesthetic room with propofol 3 mg kg^{-1} and fentanyl 2 μg kg^{-1}, and vecuronium 0.1 mg kg^{-1} was used to facilitate tracheal intubation. Anaesthesia was maintained with 66% nitrous oxide in oxygen and intermittent propofol administration while patients were moved to theatre and the tracheal tube connected to the circle system. The initial gas flows were set at 6 litre min^{-1}, with the vaporizers set to deliver 8% desflurane or 1.5% isoflurane. Initially the lungs were ventilated with a tidal volume of 10 ml kg^{-1} and a ventilatory frequency of 10 bpm. This was adjusted, as necessary, to maintain normocapnia.

The inspired and expired concentrations of desflurane or isoflurane were recorded at 1-min intervals. At the point where the expired concentration was 80%, or greater, of the set inspired concentration ($F_E/F_I = 0.8$, end-expired concentration/inspired concentration), the total

---

DAVID J. H. LEE, FRCA, DAVID L. ROBINSON, FRCA, NEIL SONI, MD, FRCA, FANZCA, Magill Department of Anaesthetics, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH. Accepted for publication: February 1, 1996.

Correspondence to N. S.

fresh gas flow was reduced to 500 ml min^{-1} with a mixture of 50 % nitrous oxide and 50 % oxygen, and the time from connection to the circle absorption system was noted. The inspired and expired values of isoflurane or desflurane continued to be monitored until the end of anaesthesia. As this study was designed to evaluate short anaesthetics, a maximum time of 25 min was chosen arbitrarily. If the anaesthetic was shorter than 25 min and *F*E/*F*I failed to reach 0.8, then the time at the end of the anaesthetic was taken as the end-point. If the anaesthetic progressed beyond 25 min yet failed to achieve an *F*E/*F*I of 0.8, then 25 min was taken as the end-point.

The Mann–Whitney *U* test was used to test the difference in times at which the flow rates could be reduced.

An Ohmeda RGM 5250 multigas analyser was used to determine end-expired values. Accuracy is described as ±0.2 % over the range 0–5 % for isoflurane and ±0.5 % over the range 5.1–10 % for desflurane. This study was approved by the Riverside Medical Ethics Committee.

Results

We studied 64 patients, 32 in the isoflurane and 32 in the desflurane group. Median age was 35 (interquartile range (IQR) 11) yr and median weight 61 (IQR 14) kg. There was no significant difference between the ages in the two groups.

All patients in the desflurane group achieved an *F*E/*F*I = 0.8 during anaesthesia. In the isoflurane group, eight patients failed to achieve *F*E/*F*I = 0.8 by 25 min and were given an arbitrary value of 25 min. There was one patient in the isoflurane group where the anaesthetic time on the circle absorption system was only 20 min and who failed to reach *F*E/*F*I = 0.8. In that situation and for the purposes of this study, the time to reach *F*E/*F*I = 0.8 was given the arbitrary value of 20 min.

The median time to *F*E/*F*I = 0.8 in the isoflurane group was 19 (IQR) 12) min and in the desflurane group 5 (IQR 1) min. The difference in the time to reducing flow was significant ($P = 0.001$, Mann–Whitney *U* test). As nine patients failed to reach *F*E/*F*I = 0.8 and were given an arbitrary value of 25 min (except for one given 20 min), the isoflurane values were artificially low so that the difference between the two agents was greater than indicated.

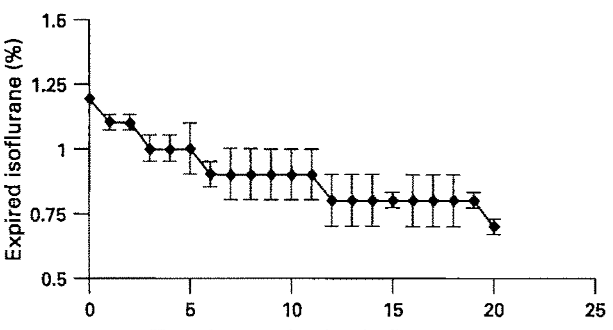


Figure 1 Expired concentration of isoflurane (mean, SD) after reduction in fresh gas flow rates to 500 ml min^{-1}. Time 0 = point at which flows were reduced.

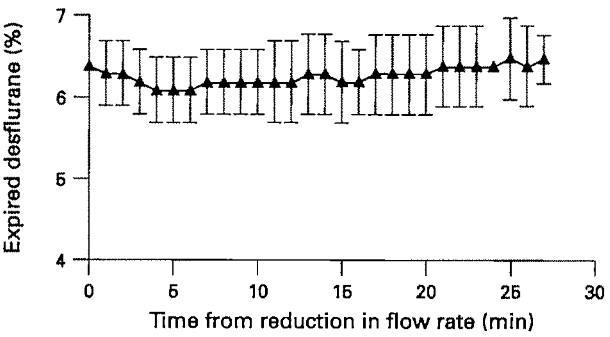


Figure 2 Expired concentration of desflurane (mean, SD) after reduction in fresh gas flow rates to 500 ml min^{-1}. Time 0 = point at which flows were reduced.

After reduction in flow rates, when *F*E/*F*I = 0.8 had been achieved, observations were made of the end-expired values of the volatile agents. The time at which the flow rate was reduced was termed time = 0 and the results plotted for isoflurane and desflurane at 1-min intervals (figs 1, 2).

Discussion

Previously it has been considered that the potential advantages of circle compared with non-rebreathing systems would be of benefit only in anaesthetics of long duration. In short anaesthetics, with the previous generation of soluble volatile agents, either high flows are required until the system has stabilized, negating the benefits of the circle, or complex and sophisticated techniques have to be used. The advent of new insoluble agents may enable the circle system to be used more efficiently in short anaesthetics, widening its effective application.

When *F*E/*F*I = 0.8 was used as an indicator to reduce the fresh gas flow into the circle system, the flows were reduced at a median time of 5 min with desflurane and 19 min with isoflurane. After the reduction in flows to a low flow of 500 ml min^{-1}, the pattern of change in the expired concentrations of desflurane and isoflurane were different. Desflurane decreased initially and then recovered while isoflurane decreased and then continued to decrease for the duration of time during which the concentration was measured, albeit a relatively short period of time in this study.

There are several aspects of this study which should be discussed. The time at which the flows were reduced was chosen in the absence of a specific indicator in the literature. An *F*E/*F*I of 0.8 was chosen for two reasons, First, it is a value which, using a multigas analyser, is easy to apply clinically with any volatile agent. Second, as it equates to 2–3 half-lives, it is an appropriate point on the uptake curve for volatile agents; the exponential curve is flattening at *F*E/*F*I = 0.8, indicating that the uptake of agent is reducing at this point (fig. 3). Uptake of agent beyond this point should be considerably less than earlier in the anaesthetic. Maintenance of the expired concentration depends on whether or not the

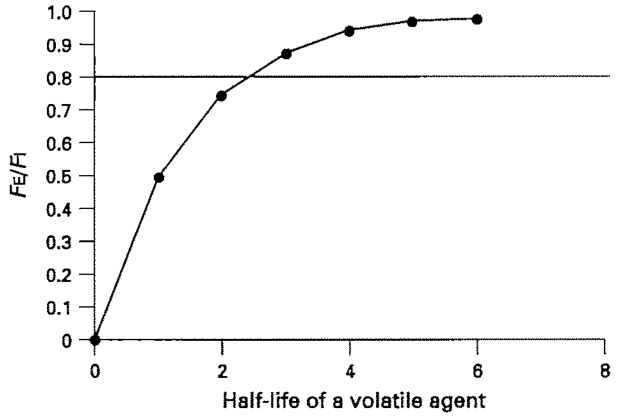


Figure 3 Theoretical curve of *FE/FI* against multiples of the half-life of a volatile agent assuming *FE* reaches *FI* eventually. *FE/FI* = 0.8 corresponds to the part of the curve with a reducing slope indicating a reduced speed of uptake.

dose of volatile agent administered in the new low flow is greater than, equal to or less than continuing uptake during the ongoing anaesthetic. In this study a flow rate of 500 ml min^{-1} was chosen as it is low by most standards, and also it delivers a small amount of anaesthetic agent accentuating any major difference in uptake between the agents. Higher flows deliver more agent and reduce the influence of flow rate on the expired values after the reduction in flow rate. The transient reduction and subsequent recovery of end-expired concentration with desflurane at low flow suggests that continuing desflurane uptake was satisfied by the small amount administered at low flow. The persistent reduction in expired values with isoflurane suggests that isoflurane uptake continued to be greater than that delivered by the low flow rates, over these relatively short-time periods. This is not unexpected given the comparative solubility of the agents and the low flow rates used.

The method of anaesthesia chosen is important when considering low-flow anaesthesia with a circle system for short anaesthetics. There are several potential problems. An adequate dose of anaesthetic agent has to be given to both prime the system and anaesthetize the patient. A continuing dose has then to be given to compensate for the continuing uptake and distribution of agent within the patient. As the volatile agent is administered as a percentage of the total fresh gas, low flows preclude a large dose being given unless a very high concentration is used. Consideration then has to be given to nitrogen washout of both the system and the patient, and the influence of nitrous oxide uptake, both early and late, on the concentrations of gases and vapours in the system. At low flows the volumes of these gases either being washed out or taken up have a relatively large impact, although any changes in concentration are easily monitored using the multigas analyser. Alternatively, the volatile agent can be injected into the circle system. The same potential difficulties with gas concentrations occur and there are technical and mathematical considerations regarding method and speed of administration [3, 4].

In this study high initial flows were used. This is in keeping with standard practice with other breathing systems. Nitrogen washout occurs rapidly and the uptake of nitrous oxide is relatively unimportant as the volumes of either gas taken up or released are trivial compared with flows into the system. The concentration of volatile agent set on the vaporizer is the concentration intended, and with the vaporizer out of circuit the set concentration represents the inspired value at high flows. When flows are reduced there is no alteration in the vaporizer settings and there is no risk of high concentration of volatile agent. The risk is of decreasing expired concentrations of volatile agents with a reduction in depth of anaesthesia. At total flows of only 500 ml min^{-1} (50% oxygen:50% nitrous oxide) the oxygen concentration must be monitored closely as over long periods it is possible for the inspired oxygen to decrease to less than 30%, even with a 50% oxygen mixture, as oxygen delivery may be close to oxygen consumption in some circumstances.

The method used in this study was deliberately attuned to anaesthesia for short surgical cases with the circle system. In patients receiving desflurane, the use of *FE/FI* = 0.8 to determine when flows could be reduced allowed the circle to be used as a low-flow system at a very early part of the anaesthetic. Using even very low flows (500 ml min^{-1}) did not cause clinical problems with decreasing expired desflurane values. With isoflurane, high flows were in use for most of the anaesthetic.

It is difficult to avoid the economic issue when discussing the circle system, in particular when using expensive agents, the cost of which prohibits introduction into many hospitals. Assuming an anaesthetic time of 20 min with the volatile agent used throughout, and fresh gas flows being reduced at the times suggested by the values obtained in this study, the cost of the volatile agents can be calculated. In this institution isoflurane would cost £3.60 and desflurane £2.60 for a 20-min anaesthetic. (At a fresh gas flow of 6 litre, the cost of desflurane would be £8.60.) The 30% difference, at low flow, has to be evaluated against the total cost of both the anaesthetic and the case [5, 6]. Of greater relevance to us is the ability to use the circle system efficiently and safely for day-case anaesthesia.

References

1. Bengtson JP, Bengtson A, Stenqvist O. The circle system as a humidifier. *British Journal of Anaesthesia* 1989; **63**: 453–457.
2. Yasuda N, Lockhart SH, Eger EI, Weiskopf RB, Johnson BH, Freire BA, Fassoulaki A. Kinetics of desflurane, isoflurane and halothane in humans. *Anesthesiology* 1991; **74**: 489–498.
3. el-Attar AM. Guided isoflurane injection in a totally closed circuit. *Anaesthesia* 1991; **46**: 1059–1063.
4. Lockwood GG, Chakrabarti MK, Whitwam JG. A computer-controlled closed anaesthetic breathing system. *Anaesthesia* 1993; **48**: 690–693.
5. Pedersen FM, Nielsen J, Ibsen M, Guldager H. Low-flow isoflurane–nitrous oxide anaesthesia offers substantial economic advantages over high- and medium-flow isoflurane–nitrous oxide anaesthesia. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 509–512.
6. Bailey CR, Ruggier R, Cashman JN. Anaesthesia: cheap at twice the price? Staff awareness cost comparisons and recommendations for economic savings. *Anaesthesia* 1993; **48**: 906–910.

British Journal of Anaesthesia 1996; **76**: 783–789

Oxygen consumption and delivery relationship in brain-dead organ donors

O. LANGERON, P. COUTURE, J. MATEO, B. RIOU, J.-L. PANSARD AND P. CORIAT

Summary

The oxygen delivery ($D\text{O}_2$) and consumption ($\dot{V}\text{O}_2$) relationship in brain-dead organ donors is unknown. Therefore, in a prospective study, we determined the $D\text{O}_2/\dot{V}\text{O}_2$ relationship in 21 consecutive brain-dead patients. Patients were allocated to one of two groups, according to plasma lactate concentration: normal (group NL, $n = 11$) or high (>2.5 mmol litre^{-1}) (group HL, $n = 10$). $\dot{V}\text{O}_2$ was measured independently, using indirect calorimetry, under control conditions, during low $D\text{O}_2$ challenge with PEEP administration, and high $D\text{O}_2$ challenge with inflation of medical antishock trousers and volume expansion or blood transfusion, as required. Under control conditions, there were no significant differences between groups NL and HL in haemodynamic or oxygenation variables, both groups having a low $\dot{V}\text{O}_2$ (mean 114 (SD 21) ml min^{-1} m^{-2}). In group HL there was a different $D\text{O}_2/\dot{V}\text{O}_2$ relationship pattern, with a dependent $\dot{V}\text{O}_2$ only. The mean slope of the $D\text{O}_2/\dot{V}\text{O}_2$ relationship was significantly higher in group HL than in group NL (0.12 (0.09) *vs* 0.04 (0.07), $P < 0.05$). We conclude that brain death was associated with a low $\dot{V}\text{O}_2$, and patients in group HL exhibited $D\text{O}_2/\dot{V}\text{O}_2$ dependency which was not observed in patients in group NL. *(Br. J. Anaesth.* 1996; **76**: 783–789)

Key words

Complications, brain death. Measurement techniques, calorimetry. Oxygen, consumption. Oxygen, delivery.

Transplantation of organs from brain-dead donors has become a common therapy for patients suffering from end-stage organ failure. Many physiological disturbances are associated with brain death, and management of the multiple organ donor is complex [1]. Failure to maintain cardiovascular and body homeostasis can induce sub-optimal organ perfusion and early graft dysfunction in the recipient [2]. However, in brain-dead patients, the optimal oxygen delivery ($D\text{O}_2$) required to meet the metabolic demand and provide appropriate tissue oxygenation is unknown. Oxygen consumption ($\dot{V}\text{O}_2$), calculated using the Fick method, has been suggested as being low in brain-dead patients [3–5]. This phenomenon could be related either to a decrease in oxygen requirements similar to that observed in anaesthetized patients [6–8] or to a deceased $D\text{O}_2$ because of hypovolaemia, left ventricular dysfunction, or both. Moreover, an abnormal $D\text{O}_2/\dot{V}\text{O}_2$ relationship could occur in brain-dead patients, as reported previously in critically ill patients [9–11]. Indeed, several studies have supported the hypothesis of a decrease in oxidative metabolism in brain-dead patients [4, 12], that could be explained by a $\dot{V}\text{O}_2$ supply dependency.

The aim of this study was to measure systemic $D\text{O}_2$ and $\dot{V}\text{O}_2$ in brain-dead patients before and after variation in $D\text{O}_2$, to determine the $D\text{O}_2/\dot{V}\text{O}_2$ relationship. To ensure an accurate and valid assessment of this relationship, $\dot{V}\text{O}_2$ and $D\text{O}_2$ were measured independently. Moreover, plasma concentrations of lactate may indicate if metabolism is predominantly aerobic or anaerobic, and has been used to assess organ donors [3, 5]. Consequently, we tested the hypothesis that the $D\text{O}_2/\dot{V}\text{O}_2$ relationship could differ, according to plasma concentrations of lactate.

Patients and methods

The study was approved by the Ethics Committee of Pitié-Salpêtrière Hospital and conducted according to French legislation concerning multiple organ procurement. Brain death was certified by: a neurological examination demonstrating the absence of brainstem reflexes; an apnoea test performed with intratrachael continuous high flow (15 litre min^{-1}) of oxygen and after 15 min of mechanical ventilation with an $F\text{I}_{\text{O}_2}$ of 100%; absence of spontaneous ventilation movement associated with an arterial $P\text{CO}_2$ greater than 8 kPa; no electrical activity during a 20-min electroencephalographic recording; absence of hypothermia (35 °C) and drugs known to depress the central nervous system [1, 5].

All patients had a stable haemodynamic state, characterized by a mean arterial pressure greater than 60 mm Hg without any change in requirements for fluids, inotropic support, or both, in the preceding hour, and without hepatic or renal failure. During the study, fluid therapy and inotropic

---

OLIVIER LANGERON*, MD, PIERRE COUTURE, MD, JOACHIM MATEO, MD, BRUNO RIOU, MD, PHD, JEAN-LOUIS PANSARD, MD, PIERRE CORIAT, MD, Department of Anesthesiology and Critical Care, Hôpital Pitié-Salpêtrière, Paris VI University, Paris, France.
Accepted for publication: January 16, 1996.

*Address for correspondence: Département d'Anesthésie-Réanimation, Hôpital Pitié-Salpêtrière, 47 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France.

support were guided by haemodynamic monitoring with a pulmonary artery catheter, urinary output and laboratory estimation of plasma concentrations of electrolytes [5]. All patients were ventilated mechanically with an FI_{O_2} of 40% to maintain $Pa_{O_2} > 13$ kPa, Pa_{CO_2} at 4.5–5.3 kPa and pH at 7.35–7.45. Oesophageal temperature was maintained greater than 35.5 °C using heated blankets and perfusion warming.

MEASUREMENTS

Haemodynamic measurements were obtained via an indwelling radial artery catheter and a pulmonary artery catheter (SP5507 S, Viggo-Spectramed, Montigny le Bretonneux, France) connected to a haemodynamic monitor (HP 78354, Hewlett-Packard, Andover, MA, USA). The following haemodynamic variables were measured: heart rate (HR), mean arterial pressure (MAP), mean pulmonary arterial pressure (MPAP) and pulmonary capillary wedge pressure (PCWP). Cardiac output was measured in triplicate using the thermodilution method, and the mean was calculated. Systemic vascular resistance (SVR) and cardiac index (CI) were calculated according to standard formulae. Transoesophageal echocardiography (HP Sonos 1500, Hewlett-Packard, Andover, MA, USA) was performed by a trained echocardiographer and left ventricular ejection fraction area (LVEFa) was calculated.

Plasma concentrations of lactate (normal values $\leqslant 2.5$ mmol litre^{-1}) were measured in control conditions using an enzymatic method (Dimension apparatus, Dupont de Nemours, Wilmington, DL, USA). As an increase in plasma concentrations of lactate is thought to reflect a shift from oxidative to anaerobic metabolism with tissue hypoxia, brain-dead patients were divided into two groups based on whether they had a normal (NL) or high (HL) plasma lactate concentration, above 2.5 mmol litre^{-1}, in control conditions. This value was not known during the study, so that physicians performed the Do_2 challenge blinded.

Arterial and mixed venous blood was obtained to measure pH, partial pressures of oxygen (Po_2) and carbon dioxide (Pco_2), oxygen saturation (So_2) (BG Electrolytes Apparatus, Instrumentation Laboratory, Milano, Italy) and haemoglobulin (Hb) concentration (Cobas Argo, Apparatus, Roche, Basle, Switzerland). Do_2 was calculated using the following formulae:

$$Do_2 = \mathrm{CI}((1.34 \times \mathrm{Hb} \times Sa_{O_2}) + (0.003 \times Pa_{O_2})) \times 10$$

$\dot{V}o_2$ and Do_2 were measured independently to obtain reliable results, avoiding mathematical coupling of shared variables [13–16]. As reported previously [17–19], $\dot{V}o_2$ was measured using a portable indirect calorimetry system (Deltatrac, Metabolic Monitor, Datax Instrumentation Corp, Helsinki, Finland). This metabolic monitor measures carbon dioxide and oxygen concentrations in inspired and expired gases per minute and calculates carbon dioxide production and oxygen consumption during that minute. These measurements were performed on the ventilator circuit with a paramagnetic oxygen sensor, a carbon dioxide infrared analyser and a flowmeter. This system has been validated previously for accuracy, sensitivity and reproducibility in the measurement of $\dot{V}o_2$ [17, 18]. The mean error in the measurement of $\dot{V}o_2$ at baseline and after increasing $\dot{V}o_2$ is -2% (range -7 to 3%) [19]. Calibration of the apparatus was performed with a mixture of 96% oxygen and 4% carbon dioxide before each use.

For each patient, measurements were performed minute-by-minute over a 20-min period in which variation in minute-by-minute measurements of oxygen consumption was less than 5%. In each patient, during each period of the study, $\dot{V}o_2$ was determined as the mean of 20 measurements over a 20-min period. All patients were ventilated mechanically with a constant FI_{O_2} of 40% throughout the study. Oxygen extraction was calculated by dividing $\dot{V}o_2$ by Do_2:

$$\text{Oxygen extraction} = \dot{V}o_2 \times Do_2^{-1}.$$

EXPERIMENTAL DESIGN

The trachea was not suctioned and patients were not turned within the 30 min before acquisition of measurements and throughout the study. We performed a Do_2 challenge to obtain changes in Do_2 of at least $\pm 20\%$ from control Do_2.

To decrease Do_2, positive end-expiratory pressure (PEEP) was administered to decrease cardiac output. PEEP titration was performed to maintain MAP greater than 40 mm Hg. The level of PEEP was increased up to 10 or 15 cm H_2O (mean 12 (SD 4) cm H_2O). After a 15-min stabilization period, $\dot{V}o_2$ was measured.

To increase Do_2, inflation of medical antishock trousers (MAST, Jobst Ltd, OH, USA) was undertaken to increase venous return and thus cardiac output [20]. The inflation pressure was approximately 40 cm H_2O in the leg compartments and 30 cm H_2O in the abdominal compartment. These levels of inflation pressure induce venous compression without arterial compression, enabling an increase in Do_2 [20]. MAST inflation was followed by volume expansion of 500 ml of gelatin solution (Plasmion, Laboratories Roger Bellon, France) or transfusion of packed red blood cells if packed cell volume was less than 30%. This Do_2 challenge was monitored using a pulmonary artery catheter to avoid PCWP values greater than 20 mm Hg. After a 15-min stabilization period, $\dot{V}o_2$ was measured.

At the end of each 20-min period, haemodynamic and metabolic variables were recorded, and arterial and mixed venous blood was obtained for blood-gas analysis. We determined $\dot{V}o_2$ in the same order: control conditions, low Do_2 and high Do_2, with a recovery period between low and high Do_2 characterized by a stable haemodynamic and metabolic state, as in control conditions.

STATISTICAL ANALYSIS

Data are expressed as mean (SD or range). Comparison of control values between the two groups (NL and HL) was performed using the Student's *t* test and the Fisher's exact method. Comparison of several means was performed using repeated-measure analysis of variance and Newman–Keuls test. The relationship between $\dot{V}o_2$ and Do_2 was fitted to a two-regression line model. The two best-fit regression lines were determined by the sum of least squares technique [21]. The critical Do_2 represented the threshold, below which $\dot{V}o_2$ started to decrease with a further reduction in Do_2. All P values were two-tailed and $P < 0.05$ was considered significant. Statistical analysis was performed on a computer using PCSM software (V3.1, Deltasoft, Meylan, France).

Results

We studied 21 brain-dead patients (15 men), mean age 38 (range 16–53) yr. Eleven patients had a normal (group NL) plasma lactate concentration (1.9 (SD 0.4); range 1.25–2.5 mmol $litre^{-1}$), and 10 patients had an elevated (group HL) plasma lactate concentration (4.0 (0.9); 2.6–5.5 mmol $litre^{-1}$). There were no significant differences between the two groups in age, cause of brain death, mean time lapse between causal event and brain death, body temperature, haemoglobin concentration, LVEFa and the number of patients receiving dopamine throughout the study or dose of dopamine (table 1). Under control conditions, there were no significant differences in haemodynamic variables between groups NL and HL, except for cardiac index (table 2). There were no significant differences between groups for Do_2 (group NL, 428 (131); range 276–684 ml min^{-1} m^{-2} *vs* group HL, 450 (203); 190–733 ml min^{-1} m^{-2}), $S\bar{v}_{O_2}$, oxygen extraction, arterial oxygen content and the arteriovenous difference in oxygen content in control conditions (table 3). Moreover, a low $\dot{V}o_2$ was observed in the two groups (114 (21) ml min^{-2} m^{-2}) and $\dot{V}o_2$ was not significantly different between groups in control conditions (table 3).

During the Do_2 challenge, we observed a significant increase in Do_2 in both groups during MAST application (group NL, +24 (17)%, $P < 0.05$; group HL, +48 (25)%, $P < 0.05$), and a significant decrease in Do_2 in both groups during PEEP

Table 1 Patient characteristics (number of patients or mean (SD or range)). BD = Brain death, LVEFa = left ventricular ejection fraction area. No significant differences between groups

	Group NL ($n = 11$)	Group HL ($n = 10$)
Age (yr)	39 (21–53)	32 (16–51)
Sex (M/F)	8/3	7/3
Causes of BD		
Head injury	6	6
Cerebral vascular disease	3	2
Cerebral anoxia related to cardiac arrest	2	2
Time lapse between causal event and BD (h)	41 (45)	35 (42)
Dopamine		
No. of patients	8	10
Dose (μg kg^{-1} min^{-1})	4.9 (3.5)	5.0 (2.5)
LVEFa (%)	60 (15)	58 (18)
Haemoglobin (g dl^{-1})	9.4 (2.3)	9.1 (2.5)
Pa_{O_2}/FI_{O_2} (mm Hg)	341 (87)	360 (160)
Body temperature (°C)	36.7 (0.9)	37.0 (0.6)

Table 2 Haemodynamic variables in brain-dead patients with normal lactate (NL) and high lactate (HL) concentrations during oxygen delivery (Do_2) challenge (mean (SD)). MAP = Mean arterial pressure; HR = heart rate; CI = cardiac index; PAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance. *$P < 0.05$ compared with control condition

		Group NL ($n = 11$)	Group HL ($n = 10$)	Overall between-group comparison
MAP	Low Do_2	58 (11)*	53 (10)*	
(mm Hg)	Control	83 (8)	73 (12)	ns
	High Do_2	97 (16)*	102 (22)*	
HR	Low Do_2	111 (25)	114 (21)	
(beat min^{-1})	Control	107 (29)	110 (18)	ns
	High Do_2	106 (27)	114 (22)	
CI	Low Do_2	2.6 (0.7)*	2.5 (1.1)*	
(ml min^{-1} m^{-2})	Control	3.8 (1.1)	3.9 (1.6)	0.05
	High Do_2	3.8 (1.0)	5.0 (1.9)*	
PAP	Low Do_2	22 (5)*	20 (5)*	
(mm Hg)	Control	18 (7)	15 (5)	ns
	High Do_2	23 (10)*	23 (5)*	
PCWP	Low Do_2	15 (4)*	14 (4)*	
(mm Hg)	Control	7 (5)	6 (3)	ns
	High Do_2	13 (7)*	13 (3)*	
SVR	Low Do_2	18.9 (8.2)	19.8 (12.1)	
(UI)	Control	22.0 (7.3)	21.3 (10.7)	ns
	High Do_2	23.6 (6.2)	21.1 (11.8)	

Table 3 Oxygenation variables in brain-dead patients with normal lactate (NL) and high lactate (HL) concentrations during oxygen delivery (Do_2) challenge (mean (SD)). Do_2 = Oxygen delivery; $\dot{V}o_2$ = oxygen consumption; $S\bar{v}_{O_2}$ = mixed venous oxygen saturation; Ca_{O_2} = arterial oxygen content; $Ca_{O_2}-Cv_{O_2}$ = arteriovenous oxygen content difference. *$P < 0.05$ compared with control condition

		Group NL ($n = 11$)	Group HL ($n = 10$)	Overall between-group comparison
Do_2 (ml min^{-1} m^{-2})	Low Do_2	325 (108)*	277 (117)*	
	Control	428 (131)	450 (203)	ns
	High Do_2	525 (144)*	658 (293)*	
$\dot{V}o_2$ (ml min^{-1} m^{-2})	Low Do_2	98 (17)*	100 (13)*	
	Control	109 (24)	119 (16)	< 0.001
	High Do_2	104 (24)	142 (24)*	
$S\bar{v}_{O_2}$ (%)	Low Do_2	70 (12)*	67 (9)*	
	Control	79 (7)	77 (10)	ns
	High Do_2	83 (7)	79 (8)	
Oxygen extraction ratio (%)	Low Do_2	33 (12)*	42 (18)*	
	Control	27 (8)	33 (20)	ns
	High Do_2	21 (6)*	26 (14)	
Ca_{O_2} (ml 100 ml^{-1})	Low Do_2	12.3 (2.3)	12.0 (3.0)	
	Control	12.4 (3.0)	12.0 (3.1)	ns
	High Do_2	13.3 (1.8)	12.7 (2.5)	
$Ca_{O_2}-Cv_{O_2}$ (ml 100 ml^{-1})	Low Do_2	3.5 (1.4)*	3.9 (1.1)*	
	Control	2.5 (0.6)	2.7 (0.6)	ns
	High Do_2	2.0 (0.8)	2.3 (0.7)	

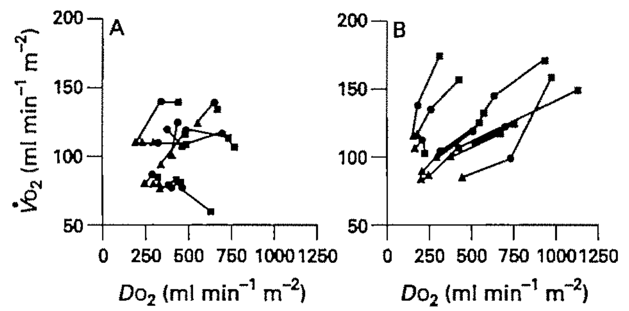


Figure 1 Individual relationship between oxygen consumption ($\dot{V}o_2$) and oxygen delivery (Do_2) during Do_2 challenge in patients with normal plasma lactate concentrations (group NL, $n = 11$) (A) and high plasma lactate concentrations (group HL, $n = 10$) (B) under three conditions: low Do_2 (▲), control Do_2 (●) and high Do_2 (■).

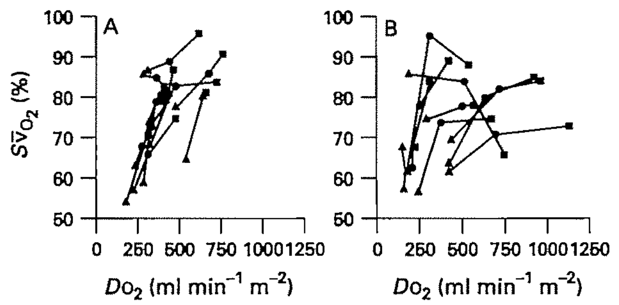


Figure 2 Individual relationship between mixed venous oxygen saturation ($S\bar{v}_{O_2}$) and oxygen delivery (Do_2) during Do_2 challenge in patients with normal plasma lactate concentrations (group NL, $n = 11$) (A) and high plasma lactate concentrations (group HL, $n = 10$) (B) under three conditions: low Do_2 (▲), control Do_2 (●) and high Do_2 (■).

administration (group NL, −24 (10)%, $P < 0.05$; group HL, −35 (12)%, $P < 0.05$). In group NL, $\dot{V}o_2$ did not increase significantly during high Do_2 challenge (−4 (8)%) and was moderately decreased during low Do_2 challenge (−9 (9)%, $P < 0.05$). In contrast, in group HL, $\dot{V}o_2$ increased significantly during high Do_2 challenge (+19 (17)%, $P < 0.05$) and decreased significantly during low Do_2 challenge (−16 (6)%, $P < 0.05$) (table 3).

There was a different pattern in the $Do_2/\dot{V}o_2$ relationship in groups NL and HL. $\dot{V}o_2$ increased with Do_2 throughout Do_2 challenge in patients in group HL, whereas patients in group NL exhibited small variations in $\dot{V}o_2$ ($\Delta\dot{V}o_2$) during control and high Do_2 conditions. Nevertheless, it should be pointed out that variations in Do_2 (ΔDo_2) were lower in group NL compared with group HL (48 (25)% *vs* 83 (26)%; $P < 0.05$). However, the magnitude of $\Delta\dot{V}o_2/\Delta Do_2$ was significantly higher in group HL than in group NL (0.13 (0.09) *vs* 0.05 (0.04); $P < 0.05$).

Individual analysis of the $Do_2/\dot{V}o_2$ relationship is depicted in figure 1. We observed a significant increase in the mean slope of the $Do_2/\dot{V}o_2$ relationship in patients in group HL compared with patients in group NL (0.12 (0.09) *vs* 0.04 (0.07); $P < 0.05$). This $Do_2/\dot{V}o_2$ relationship, either in NL or HL patients, impedes the use of a two-regression line model in each group and consequently the assessment of critical Do_2 could not be achieved in either group (fig. 1).

As shown in table 3 and figure 2, we observed a different pattern in the $S\bar{v}_{O_2}/Do_2$ relationship in groups NL and HL, with a significant correlation between $S\bar{v}_{O_2}$ and Do_2 in group NL ($r = 0.64$, $P < 0.05$), and no significant correlation in group HL ($r = 0.34$). The mean slope of the $S\bar{v}_{O_2}/Do_2$ relationship (fig. 2) was not significantly different between patients in groups NL and HL (0.07 (0.05) *vs* 0.05 (0.05) % ml^{-1} min m^2).

Discussion

In this study, we observed a low $\dot{V}o_2$ in brain-dead patients, both in group NL and group HL (table 3), and a different pattern in the $Do_2/\dot{V}o_2$ relationship between these two groups. Pathological $\dot{V}o_2$ dependency was noted in patients with elevated plasma concentrations of lactate and a physiological $Do_2/\dot{V}o_2$ relationship with a plateau was observed in patients with normal plasma lactate concentration.

Brain-dead patients had low $\dot{V}o_2$ values, as reported previously in normal humans at rest [8] (range of 110–150 ml min^{-1} m^{-2}) or in critically ill surgical patients undergoing mechanical ventilation at rest (114 (18) ml min^{-1} m^{-2}) or at a low level of activity (131 (21) ml min^{-1} m^{-2}) [22]. Moreover, in our study, $\dot{V}o_2$ values were close to those found in anaesthetized patients, where $\dot{V}o_2$ reached a plateau at 109 (16) ml min^{-1} m^{-2} or at 105 (13) ml min^{-1} m^{-2}, before and after cardiopulmonary bypass, respectively [6, 7]. During general anaesthesia, oxygen consumption decreased by 25–30% [8, 23], corresponding to the values found in our study during brain death. Mechanical ventilation decreases oxygen consumption and minimizes oxygen uptake. Consequently, similar $\dot{V}o_2$ values were observed during brain death and general anaesthesia [23].

The $Do_2/\dot{V}o_2$ relationship has been studied under many circumstances [24–27], but is often a source of controversy, mainly because an artefactual correlation between Do_2 and $\dot{V}o_2$ can occur by sharing common data for cardiac output and arterial oxygen content leading to mathematical coupling of these variables [13, 16, 28]. In our study, $\dot{V}o_2$ was measured independently in order to avoid this pitfall. We used the gas exchange method to measure $\dot{V}o_2$ with a metabolic monitor which had been validated previously [17, 18] and exhibits a small error in $\dot{V}o_2$ measurement when $F_{I_{O_2}}$ is less than the critical level of 75% [18]. In our study, $F_{I_{O_2}}$ was maintained constant at 40%. The second criterion for a reliable $Do_2/\dot{V}o_2$ relationship is to minimize spontaneous and provoked variations in metabolic demand with no muscle activity to keep $\dot{V}o_2$ constant. These conditions are achieved in brain death. Moreover, the $Do_2/\dot{V}o_2$ relationship may be influenced by body temperature [29]. In our study we did not observe any significant difference in temperatures between groups NL and HL which could explain the different pattern of the $Do_2/\dot{V}o_2$ relationship. Furthermore, we performed a Do_2 challenge with PEEP administration, fluid loading and MAST application, sometimes associated with blood transfusion. As reported previously, $\dot{V}o_2$ is not affected by any of these manoeuvres [16, 30]. Whereas the effects of catecholamines on cellular oxidative metabolism increase $\dot{V}o_2$ [10], dopamine is not thought to increase $\dot{V}o_2$ at the low doses used in our study [16, 31]. Moreover, we did not observe any significant difference in dopamine doses between the two groups. Finally, to ascertain that a reliable $Do_2/\dot{V}o_2$ relationship could be obtained it is necessary to have at least two data pairs for each patient over a wide range of Do_2 values. We collected three data pairs for each patient over a Do_2 variation of at least ±20% of control values, which was our minimal end-point in the Do_2 challenge (table 3). As reported previously, these different factors are essential to describe a reliable $Do_2/\dot{V}o_2$ relationship [15].

After Do_2 challenge, we observed that patients in group HL had a different $Do_2/\dot{V}o_2$ relationship pattern compared with patients in group NL (fig. 1). In group HL, the increased plasma lactate concentration suggested inadequate Do_2 and that tissue oxygen requirements were no longer satisfied, and $Do_2/\dot{V}o_2$ dependency was observed. Inadequate Do_2 usually implies either hypoperfusion or arterial desaturation, whereas impaired oxygen utilization by the tissues reflects abnormal oxygen metabolism or dysoxia [15]. However, the lack of significant differences in haemodynamic and echocardiographic data, and blood-gas analysis between the two groups suggest dysoxia in group HL, with a weak oxygen extraction and utilization by the tissues in group HL, as suggested by the non-significant difference in arteriovenous oxygen content difference between groups HL and NL. Furthermore, in group HL, the inability to obtain a critical Do_2 despite a wide Do_2 challenge with $\dot{V}o_2$ dependency would suggest a pathological $Do_2/\dot{V}o_2$ dependency [24]. In group NL, we probably did not decrease Do_2 as much as necessary to obtain critical Do_2 from which $\dot{V}o_2$ begins to decrease, with a further reduction in Do_2. Thus our results suggest that critical Do_2 in brain-dead patients with normal plasma lactate concentration was less than 330 ml min^{-1} m^{-2} which is the critical Do_2 reported in patients during general anaesthesia [6, 7]. Conversely, critical Do_2 in brain-dead patients with elevated plasma concentrations of lactate was not reached despite high Do_2 levels, and remains unknown at present.

This pathological $Do_2/\dot{V}o_2$ dependency has been reported in sepsis [10], adult respiratory distress syndrome (ARDS) [11], or both [9]. However, other recent studies in sepsis [13, 19, 20] and ARDS [14, 32] did not confirm this $Do_2/\dot{V}o_2$ dependency, probably because $\dot{V}o_2$ was measured and not calculated. Thus, this is the first time that a $Do_2/\dot{V}o_2$ dependency has been demonstrated using independent measures of Do_2 and $\dot{V}o_2$.

Our study indicated the occurrence of dysoxia in some brain-dead patients, but did not enable us to determine precisely the mechanism(s) of these abnormalities. However, several hypotheses might be suggested: (1) the event causing brain death or brain death itself is able to release mediators or induce neurohumoral dysfunction altering the microcirculation, with oxygen diffusion impairment or microcirculatory mismatch, such as during sepsis, causing dysoxia; (2) a switch from aerobic to anaerobic metabolism caused by haemodynamic deterioration occurring during brain death may induce an oxygen debt in some patients and this debt may be paid off with increasing Do_2. However, our study was conducted under stable haemodynamic conditions, several hours after resuscitation, and therefore this hypothesis is unlikely; (3) a reduction in circulating free triiodothyronine, as noted previously in brain-dead patients [3, 12], may result in decreased oxidative metabolism. Indeed, it has been shown recently that high plasma lactate concentrations are associated with mitochondrial impairment in oxygen metabolism in brain-dead patients [33].

Several limitations should be discussed to assess the clinical relevance of our study. First, systemic

$D\mathrm{o}_2$ does not assess the effectiveness of regional $D\mathrm{o}_2$ in different organs and vascular beds [26]. Local and regional blood flow redistribution are important determinants of the adequacy of both regional and systemic oxygen uptake, as reported previously [34]. Brain death is associated with loss of peripheral vasomotor tone and an inability to redistribute blood flow appropriately [1]. Consequently, brain death may also modify the local or regional $D\mathrm{o}_2/\dot{V}\mathrm{o}_2$ relationship, leading to potential organ impairment, despite appropriate systemic $D\mathrm{o}_2$. Second, elevated plasma lactate concentration might not always reflect tissue hypoxia, as lactate concentration results from the balance between lactate production and hepatic and renal clearance, the washout phenomenon after successful resuscitation, and from the activity of pyruvate dehydrogenase which may be inhibited as in sepsis. Nevertheless, in our study, none of the patients with elevated plasma lactate concentrations had hepatic or renal failure. Lastly, some authors [35] have supported the theory of obtaining supranormal values of $D\mathrm{o}_2$ to prevent dysoxia and organ system dysfunction in order to decrease mortality in critically ill patients. But a recent study failed to demonstrate any survival benefit from obtaining supranormal $D\mathrm{o}_2$ values [36]. In the management of organ donors, increasing $D\mathrm{o}_2$ in patients in group HL seems reasonable, but increasing $D\mathrm{o}_2$ to supranormal values has yet to be demonstrated. However, our results do not provide evidence that increasing $D\mathrm{o}_2$ may actually decrease plasma concentrations of lactate and that transplantation outcome could be modified by decreasing plasma lactate concentrations. Further studies are required to confirm this hypothesis.

Acknowledgements

We thank G. Annat, Professor of Physiology, Hôpital E. Herriot, Lyons, France.

References

1. Robertson KM, Cook DR. Perioperative management of the multiorgan donor. *Anesthesia and Analgesia* 1990; **70**: 546–556.
2. Grundman R, Kammerer B, Franke E, Pichlmaier H. Effect of hypotension on the results of kidney storage and the use of dopamine under these conditions. *Transplantation* 1981; **32**: 184–187.
3. Sztark F, Thicoïpe M, Masson F, Lassié P, Favarel-Garrigues JF, Petit-Jean ME. Metabolic status of brain-dead patients managed for organ procurement. *Transplantation Proceedings* 1993; **25**: 3171–3172.
4. Depret J, Teboul JL, Bensadoun H, Benoit G, Richard C. Mise en évidence d'une hypoxie tissulaire par trouble de l'extraction périphérique de l'oxygène des sujets en état de mort cérébrale. *La Presse Médicale* 1991; **20**: 1989–1990.
5. Riou B, Kalfon P, Arock M, Goarin JP, Saada M., Viars P. Cardiovascular consequences of severe hypophosphataemia in brain-dead patients. *British Journal of Anaesthesia* 1995; **74**: 424–429.
6. Shibutani K, Komatsu T, Kubal K, Sanchala V, Kumar V, Bizzari D. Critical level of oxygen delivery in anesthetized man. *Critical Care Medicine* 1983; **11**: 640–643.
7. Komatsu T, Shibutani K, Kazufumi O, Kumar K, Kubal K, Sanchala V, Lees DE. Critical level of oxygen delivery after cardiopulmonary bypass. *Critical Care Medicine* 1987; **15**: 194–197.
8. Buran MJ. Oxygen consumption. In: Snyder JV, Pinsky MR, eds. *Oxygen Transport in the Critically Ill.* Chicago: Year Book Medical Publishers, 1987; 16–21.
9. Bihari D, Smithies M, Gimson A, Tinker J. The effects of vasodilatation with prostacyclin on oxygen delivery and uptake in critical ill patients. *New England Journal of Medicine* 1987; **317**: 397–403.
10. Gilbert EM, Haupt MT, Mandanas RY, Huaringa AJ, Carlson RW. The effect of fluid loading, blood transfusion, and catecholamine infusion on oxygen delivery and consumption in patients with sepsis. *American Review of Respiratory Disease* 1986; **134**: 873–878.
11. Danek SJ, Lynch JP, Weg JG, Dantzker DR. The dependence of oxygen uptake on oxygen delivery in the adult respiratory distress syndrome. *American Review of Respiratory Disease* 1980; **122**: 387–395.
12. Novitzky D, Cooper DKC, Morell D, Isaacs S. Change from aerobic to anaerobic metabolism after brain death, and reversal following triiodothyronine therapy. *Transplantation* 1988; **45**: 32–36.
13. Vermeij CG, Feenstra BWA, Bruining HA. Oxygen delivery and oxygen uptake in postoperative and septic patients. *Chest* 1990; **98**: 415–420.
14. Ronco JJ, Phang PT, Walley KR, Wiggs B, Fenwick JC, Russell JA. Oxygen consumption is independent of changes in oxygen delivery in severe adult respiratory distress syndrome. *American Review of Respiratory Disease* 1991; **143**: 1267–1273.
15. Pinsky MR. Beyond global oxygen supply–demand relations: in search of measures of dysoxia. *Intensive Care Medicine* 1994; **20**: 1–3.
16. Hanique G, Dugernier T, Laterre PF, Dougnac A, Roeseler J, Reynaert MS. Significance of pathologic oxygen supply dependency in critically ill patients: comparison between measured and calculated methods. *Intensive Care Medicine* 1994; **20**: 12–18.
17. Ronco JJ, Phang PT. Validation of an indirect calorimeter to measure oxygen consumption in critically ill patients. *Journal of Critical Care* 1991; **6**: 36–41.
18. Takala J, Keinanen O, Vaisanen P, Kari A. Measurements of gas exchange in intensive care: laboratory and clinical validation of a new device. *Critical Care Medicine* 1989; **17**: 1041–1047.
19. Ronco JJ, Fenwick JC, Tweeddale MG, Wiggs BR, Phang PT, Cooper DJ, Cunningham KF, Russell JA, Walley KR. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *Journal of the American Medical Association* 1993; **270**: 1724–1730.
20. Mira JP, Fabre JE, Baigorri F, Coste J, Annat G, Artigas A, Nitenberg G, Dhainaut JFA. Lack of oxygen supply dependency in patients with severe sepsis. A study of oxygen delivery increased by military antishock trousers and dobutamine. *Chest* 1994; **106**: 1524–1531.
21. Samsel RW, Schumacker PT. Determination of the critical O_2 delivery from experimental data: sensitivity to error. *Journal of Applied Physiology* 1988; **64**: 2074–2082.
22. Weissman C, Kemper M. The oxygen uptake–oxygen delivery relationship during ICU interventions. *Chest* 1991; **99**: 430–435.
23. Viale JP, Annat G, Lehot JJ, Quard S, Quintin L, Parlow J, Durand PG, Zabot JM, Villard J, Estanove S. Relationship between oxygen uptake and mixed venous oxygen saturation in the immediate postoperative period. *Anesthesiology* 1994; **80**: 278–283.
24. Schumaker PT, Cain SM. The concept of a critical oxygen delivery. *Intensive Care Medicine* 1987; **13**: 223–229.
25. Dantzker DR, Foresman B, Gutierrez G. Oxygen supply and utilization relationships. *American Review of Respiratory Disease* 1991; **143**: 675–679.
26. Pinsky MR, Schlichtig R. Regional oxygen delivery in oxygen supply–dependent states. *Intensive Care Medicine* 1990; **16**: S169–S171.
27. Vincent JL. The relationship between oxygen demand, oxygen uptake, and oxygen supply. *Intensive Care Medicine* 1990; **16**: S145–S148.
28. Archie JP. Mathematic coupling of data: a common source of error. *Annals of Surgery* 1990; **193**: 296–303.
29. Schumaker PT, Rowland J, Saltz S, Nelson DP, Wood LDH.

Effects of hyperthermia and hypothermia on oxygen extraction by tissues during hypovolemia. *Journal of Applied Physiology* 1987; **63**: 1246–1252.

30. Pepe PE, Culver BH. Independently measured oxygen consumption during reduction of oxygen delivery by positive end-expiratory pressure. *American Review of Respiratory Disease* 1985; **132**: 788–792.
31. Chiolero R, Flatt JP, Revelly JP, Jequier E. Effects of catecholamines on oxygen consumption and oxygen delivery in critically ill patients. *Chest* 1991; **100**: 1676–1684.
32. Annat G, Viale JP, Percival C, Froment M, Motin J. Oxygen delivery and uptake in adult respiratory distress syndrome. *American Review of Respiratory Disease* 1986; **133**: 999–1001.
33. Sztark F, Thicoïpe M, Masson F, Lassié P, Favarel-Garrigues JF, Petit-Jean ME. Modifications du métabolisme oxydatif au cours de la mort cérébrale. *Annales Françaises d'Anesthésie et de Réanimation* 1994; **13**: R266.
34. Schlichtig R, Kramer DJ, Pinsky MR. Flow redistribution during progressive hemorrhage is a determinant of critical O_2 delivery. *Journal of Applied Physiology* 1991; **70**: 169–178.
35. Shoemaker WC, Appel PL, Kram HR, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high risk surgical patients. *Chest* 1988; **94**: 1176–1186.
36. Hayes MA, Timmins AC, Yau EHS, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *New England Journal of Medicine* 1994; **330**: 1717–1722.

British Journal of Anaesthesia 1996; **76**: 790–794

Sepsis-induced vasoparalysis does not involve the cerebral vasculature: indirect evidence from autoregulation and carbon dioxide reactivity studies

B. F. MATTA AND P. J. STOW

Summary

We have studied cerebral autoregulation and vasoreactivity to carbon dioxide in 10 patients with the sepsis syndrome receiving intensive therapy. All patients were sedated with infusions of midazolam and fentanyl, and their lungs were ventilated mechanically with oxygen–air to maintain normoxia and normocapnia. Inotropic support and antibiotics were administered as necessary. During a period of constant level of sedation and stable haemodynamics, cerebral autoregulation was tested by increasing mean arterial pressure (MAP) by 23 (SD 2) mm Hg from baseline with an infusion of phenylephrine and simultaneously recording middle cerebral artery blood flow velocity (*v*mca) using transcranial Doppler ultrasonography. Carbon dioxide reactivity was tested by varying Pa_{CO_2} between 3.0 and 7.0 kPa and simultaneously recording *v*mca. There was no significant change in *v*mca (57 (22) and 59 (23) cm s^{-1}) during the increase in MAP (75 (11) to 98 (10) mm Hg). The mean index of autoregulation (IOR) was 0.92 (SEM 0.03), which was not significantly different from 1, indicating near perfect autoregulation. Although absolute carbon dioxide reactivity was lower than reported previously in awake subjects, relative carbon dioxide reactivity was within normal limits for all patients (11.6 (SEM 0.8) cm s^{-1} and 20.3 (3) % kPa^{-1}, respectively). We conclude that cerebral carbon dioxide reactivity and pressure autoregulation remained intact in patients with the sepsis syndrome, providing indirect evidence that at least in the early stages of the syndrome, the widespread sepsis-induced vasoparalysis does not involve the cerebral vasculature. (*Br. J. Anaesth.* 1996; **76**: 790–794)

Key words

Brain, carbon dioxide, reactivity. Brain, blood flow. Measurement techniques, ultrasound. Intensive care. Complications, sepsis syndrome.

Sepsis continues to be a common and frequently fatal illness in humans. Although the pathophysiology of generalized sepsis is complex and not yet fully explained, the syndrome is generally associated with multisystem organ impairment and decreased systemic vascular resistance as a result of widespread vasoparalysis [1, 2].

Cerebral pressure autoregulation and carbon dioxide reactivity are dependent on intact cerebral vascular tone and reactivity [3]. It is not known if the vasoparalysis in patients with sepsis involves the cerebral vasculature, and if so, what effect this has on these two important mechanisms for the control of cerebral blood flow (CBF). In this study we aimed to establish if there were disturbances in cerebral autoregulation and carbon dioxide reactivity in patients with the sepsis syndrome. If this were the case, it might explain the pathophysiology of the encephalopathy seen in up to 70% of patients with sepsis, which has been associated with higher mortality [4, 5]. Furthermore, the information may be beneficial in the management of these patients in whom involvement of the cardiovascular and respiratory systems often leads to arterial pressure instability and carbon dioxide retention.

Patients and methods

After obtaining Human Subjects Committee approval and informed consent from the next of kin, we examined cerebral autoregulation and carbon dioxide reactivity in 10 patients admitted to our intensive care unit with the sepsis syndrome (eight intra-abdominal sepsis, two pneumonias) and altered mental state (confusion or delerium). The sepsis syndrome was diagnosed according to criteria described previously by Bone and colleagues [2] (table 1). Patients who had a pre-existing neurological disease and those receiving psychotropic drugs were excluded. All studies were performed within 24 h of admission to the intensive care unit. Routine monitors included electrocardiography, invasive arterial pressure, central venous and pulmonary artery pressures, and pulse oximetry. All patients received infusions of midazolam 100–300 µg kg^{-1} h^{-1} and fentanyl 1–5 µg kg^{-1} h^{-1} to maintain adequate sed-

---

BASIL F. MATTA*, MB, FRCA, PETER J. STOW, MB, FRCA, Department of Anaesthesia, Ipswich Hospital, Heath Road, Ipswich, Suffolk IP4 5PD. Accepted for publication: January 25, 1996.

*Current address for correspondence: Department of Anaesthesia, Addenbrooke's Hospital, Hills Road, Cambridge CB5 2QQ.

Table 1 Criteria for definition of the sepsis syndrome [2]

- A systemic response to infection with:
  - Hypothermia < 35.1 °C or hyperthermia > 38.3 °C
  - Tachycardia > 90 beat min^{-1} in the absence of hypovolaemia or beta-adrenergic block
  - Tachypnoea > 20 b.p.m. or requirement for ventilatory support
  - Clinical evidence of an infection site
- At least one end-organ showing evidence of inadequate perfusion or dysfunction:
  - Poor or altered cerebral function (inattention, confusion, disorientation, delirium, coma)
  - Hypoxaemia Pa_{O_2} < 10 kPa breathing room air, not caused by overt pulmonary disease
  - Elevated plasma lactate > 2.2 mmol $litre^{-1}$
  - Oliguria (urine output < 30 ml h^{-1}) without corrective therapy for at least 1 h

ation. The lungs were ventilated mechanically with oxygen–air to maintain normoxia and normocapnia. Inotropic support and antibiotics were administered as indicated clinically. During a period of constant level of sedation and stable haemodynamics, cerebral blood flow velocity (*v*mca) was measured by insonating the middle cerebral artery (MCA) using a transcranial Doppler probe (Scimed, Bristol, UK or Neuroguard, Fremont, CA, USA). One type of probe was used throughout the study for each individual patient. The methodology has been reported previously [3]. Briefly, the probe was secured in position so that the angle of insonation remained constant throughout the study. Doppler signals from the right MCA were identified and measured at a depth of 45–50 mm. The shift in frequency spectra of the Doppler signals converted into time-mean flow velocity (*v*mca) were displayed on a video monitor. A phenylephrine infusion (100 μg ml^{-1}) was used to increase mean arterial pressure (MAP) by approximately 20 mm Hg from baseline and *v*mca was recorded simultaneously. The infusion of phenylephrine was then discontinued and MAP was allowed to return to baseline. Carbon dioxide reactivity was then tested by varying Pa_{CO_2} between 3.0 and 7.0 kPa and simultaneously recording *v*mca. Arterial Pa_{CO_2} was varied, altering minute ventilation without significant change in airway pressure (changing ventilatory rate at constant tidal volume). A minimum period of 5 min was allowed for stabilization (unchanged end-tidal carbon dioxide) at each Pa_{CO_2} before measurements were made. Three paired Pa_{CO_2}–*v*mca data were obtained for each patient.

DATA ANALYSIS

The index of autoregulation (IOR) was calculated as the ratio of percentage change in estimated cerebral vascular resistance (CVRe) to percentage change in MAP, using the equations CVRe = MAP/*v*mca and IOR = %∂CVRe/%∂MAP, where MAP = mean arterial pressure at the time of *v*mca measurement [6]. Perfect autoregulation is present when the percentage change in CVRe is equal to the percentage change in MAP; no change in *v*mca with change in MAP, and IOR = 1. An IOR of 0 signifies complete absence of autoregulation. Based on studies published previously [6, 7], we considered a 15% change in IOR to be clinically insignificant. We then performed a power analysis which indicated that for a power of 0.80, an alpha value of 0.05 and a beta value of 0.20, the required number of patients to reject the null hypothesis was 10. The computed IOR and data recorded before and after the phenylephrine-induced increase in MAP were analysed using Student's *t* test. $P < 0.05$ was considered statistically significant.

To determine carbon dioxide reactivity, regression lines were constructed for paired Pa_{CO_2}–*v*mca data for each patient. Carbon dioxide reactivity was expressed in both absolute (change in *v*mca per kPa change in Pa_{CO_2}) and relative (percentage change in *v*mca at Pa_{CO_2} 5.3 kPa per kPa change in Pa_{CO_2}) values.

Results

Patient characteristics are shown in table 2. There were no significant changes in body temperature, haemoglobin concentration and partial pressure of oxygen (Pa_{O_2}) in arterial blood during the study (table 3). There was no change in Pa_{CO_2} during the autoregulation part of the study and no change in MAP during the carbon dioxide reactivity part of the study.

There was no significant change in mean *v*mca (57 (SD 22) and 59 (23) cm s^{-1}) during the increase in MAP (75 (11) to 98 (10) mm Hg). Mean IOR was 0.92 (SEM 0.03), which was not significantly different from 1, indicating near perfect autoregulation. The dose of phenylephrine required to increase MAP by approximately 20 mm Hg was 100–300 μg.

Linear regression analysis demonstrated a close relationship between *V*mca and Pa_{CO_2}, with correlation coefficients greater than 0.85 in all instances ($P < 0.001$). Although absolute cerebral vasoreactivities to carbon dioxide derived by linear regression analysis were lower than reported awake values, relative cerebral vasoreactivity to carbon dioxide was within normal limits for all patients (11.6

Table 2 Patient data (mean (SD or range))

Age (yr)	60 (21–86)
Weight (kg)	74 (17)
Sex (M:F)	4:6
Admission APACHE score	23 (18–34)
Haemoglobin (g dl^{-1})	12 (2)
Temperature (°C)	38.0 (37.0–39.0)
Cardiac index (litre min^{-1} m^{-2})	4.85 (2.93–6.60)
Systemic vascular resistance index (dyn s cm^{-5} m^{-2})	1049 (628–1501)

Table 3 Data (mean (SD)) during pressure autoregulation. ** $P < 0.01$ compared with baseline (*t* test)

	Baseline	Autoregulation
MAP (mm Hg)	75 (11)	98 (10)**
HR (beat min^{-1})	95 (36)	92 (35)
Pa_{CO_2}(kPa)	4.7 (0.3)	4.8 (0.3)
Pa_{O_2}(kPa)	13.3 (1.8)	13.4 (1.8)
*v*mca (cm s^{-1})	57 (22)	59 (23)

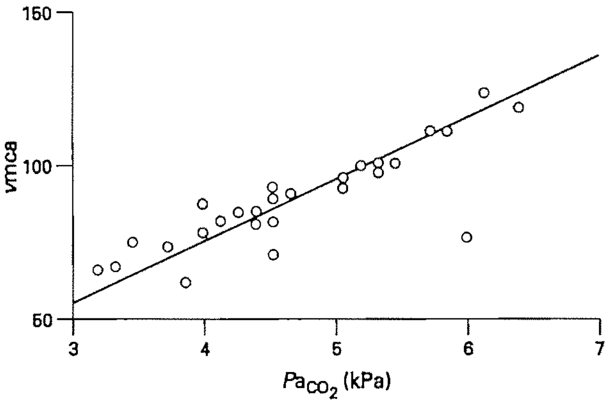


Figure 1 Relative middle cerebral artery velocity (*v*mca) *vs* corresponding Pa_{CO_2} for all patients. Relative *v*mca was calculated by expressing flow velocity values as a percentage of *v*mca at a Pa_{CO_2} of 5.3 kPa. The respective linear regression is shown.

(SEM 0.8) cm s^{-1} kPa^{-1} and 20.3 (3) % kPa^{-1}, respectively. Figure 1 shows the relative cerebral vasoreactivity for all patients (relative *v*mca *vs* Pa_{CO_2}).

Discussion

In this study, we have shown that cerebral pressure autoregulation and vasomotor reactivity to carbon dioxide remained intact in patients with the sepsis syndrome. This suggests that at least in the early stages of sepsis, the widespread sepsis-induced vasoparalysis does not involve the cerebral vasculature.

Steady-state conditions were maintained during both parts of the study. There was no change in patient body temperature or haemoglobin concentration; MAP was maintained constant during the carbon dioxide reactivity part of the study, and Pa_{CO_2} was unchanged between normotension and phenylephrine-induced hypertension phases. The drugs used for sedation (fentanyl and midazolam) have no direct cerebrovascular effects [8, 9].

Transcranial Doppler ultrasonography (TCD) is a particularly suitable tool for assessing cerebral vasoreactivity to carbon dioxide [10]. The device is inexpensive, non-invasive and non-radioactive. Multiple paired measurements can be obtained and linear regression lines constructed more accurately than with a limited number of conventional blood flow measurements [10–12]. Furthermore, despite TCD not providing a direct measure of CBF, it provides an accurate measure of relative changes in CBF [10–12]. There is now ample direct and indirect evidence to support the contention that MCA is a conductance vessel and its diameter does not change significantly with changes in arterial pressure, Pa_{CO_2} or the use of anaesthetic or vasoactive agents [11–16]. Changes in cerebral vascular resistance occur primarily through dilatation of arterioles and not the arteries of the circle of Willis [17].

Although the absolute carbon dioxide reactivity values in this study were slightly lower than reported awake values, they were consistent with values obtained during sedation and anaesthesia [6, 18, 19]. When the carbon dioxide reactivity values were normalized to *v*mca at Pa_{CO_2} 5.3 kPa, the percentage change in *v*mca per kPa approximated the awake value. Normalizing all *v*mca values by expressing them as a percentage of vmca at a Pa_{CO_2} of 5.3 kPa allows comparisons with previously published studies and reduces the dependence on the baseline *v*mca value, which is reported to vary between 30 and 90 cm s^{-1} in awake individuals [20]. Bowtón and colleagues have shown that in septic patients, CBF is reduced [21]. Although it is not possible to estimate absolute CBF accurately, *v*mca values obtained in this study were within the normal range.

We could only estimate cerebral vascular resistance (CVRe) because we measured *v*mca and not absolute CBF. This estimation of CVRe depends on our previous assumption that changes in CBF correlate with changes in *v*mca. We then calculated the index of autoregulation by dividing the percentage change in CVRe by the percentage change in MAP. An IOR of 1 indicates that the percentage change in CVRe is the same as the percentage change in MAP and no change in CBF results (complete autoregulation). Complete absence of autoregulation gives an IOR of 0. IOR was 0.92 (SEM 0.03), which indicated that near complete autoregulation was present in patients with the sepsis syndrome. This deviation from an IOR of 1 is clinically unimportant and within normal limits, as dynamic autoregulation in normal volunteers has been shown to have an SD of 15% [22]. Power analysis ensured that 10 patients were sufficient to reject the null hypothesis with a power of 0.80, an alpha error of 0.05 and a beta error of 0.20.

Although we only examined autoregulation in one direction (increase in pressure), we chose a level of MAP which normally lies in the middle of the autoregulation curve. Therefore, there is no reason to assume that a decrease instead of an increase in MAP would have yielded different results. This has been confirmed recently by Tiecks and colleagues who found that the ability of the cerebral circulation to autoregulate is similar whether MAP is increased or decreased [23].

Encephalopathy may be present in up to 70% of patients with sepsis [4]. The severity ranges from impaired attention and concentration to delirium and coma. The electroencephalograph (EEG) is a valuable tool in the intensive care of these patients. The EEG is a sensitive indicator of the severity of the encephalopathy. Four main patterns of increasing severity are seen: diffuse theta, intermittent rhythmic delta, triphasic waves, and suppression or burst suppression [24]. Although EEG patterns and the clinical grade of encephalopathy may be associated with a poor outcome, complete recovery is possible despite the presence of suppression and burst suppression EEG patterns [24, 25]. All patients in this study had a mild degree of encephalopathy and made a complete recovery. The size of the study does not allow speculation on the grade of the encephalopathy, autoregulation and carbon dioxide reactivity, and outcome.

The pathogenesis of septic encephalopathy is unknown. A reversible "metabolic" mechanism has been proposed to explain the presence of encephalopathy without direct infection of the brain and without consistent neuropathological changes [4]. Cytokines, the chemical messengers released from macrophages and lymphocytes, are likely to be responsible for this "metabolic" derangement, with increased permeability of the blood–brain barrier, increased capillary leakage and tissue oedema, interference with microcirculation, increased procoagulant activity, and direct effects on tissue metabolism [24–26]. Cytokines (interleukin-1 and-2) may also directly affect the brain [26–29]. There is evidence to suggest that at least in animals, there is differential impairment of pulmonary and systemic vascular contractility in hyperdynamic sepsis [30]. Robert and colleagues have shown that interleukin-1, a cytokine released during septic shock, reduces the noradrenaline-induced arterial vessel contraction in rabbit renal and pulmonary beds, but not in hepatic vessels [31]. This hyporeactivity may affect the mechanisms regulating cerebral blood flow, cerebral autoregulation and vasoreactivity to carbon dioxide, which are dependent on the ability of the cerebral vasculature to regulate its tone. In this study, we have shown that in patients without severe encephalopathy, these mechanisms remained intact. Although the exact mechanisms responsible for autoregulation and vasoreactivity to carbon dioxide remain unclear, this study suggests that cerebral vessels were not hyporeactive to changes in MAP or Pa_{CO_2}. However, carbon dioxide reactivity and autoregulation studies were performed during a period of optimal systemic haemodynamic state (table 2), with patients receiving vasoactive agents (dobutamine, dopamine and noradrenaline) that theoretically could have been responsible for restoring cerebrovascular reactivity. Although it is important to identify if these mechanisms are affected by the disease process, or if they can be restored by optimizing systemic haemodynamic state, it is at least reassuring that when systemic haemodynamics are optimized, the cerebral circulation is able to respond to changes in arterial pressure and carbon dioxide tension. This is important for the management of those patients in whom the involvement of the cardiovascular and respiratory systems often leads to arterial pressure instability and carbon dioxide retention.

Acknowledgement

We thank Neuroguard, Fremont, USA, for providing the transcranial Doppler device.

References

1. Glaucer MP, Zanetti G, Baumgartner J-D, Cohen J. Septic shock: pathogenesis. *Lancet* 1991; **338**: 732–736.
2. Bone RC, Fisher CJ, Clemmer TP, Slotman GJ, Metz CA, Balk RA. The Methylprednisolone Severe Sepsis Study Group. Sepsis syndrome: a valid clinical entity. *Critical Care Medicine* 1989; **17**: 389–393.
3. Strebel S, Lam AM, Matta BF, Mayberg TS, Newell DW. The effect of isoflurane, desflurane and propofol on cerebrovascular pressure autoregulation in humans. *Anesthesiology* 1995; **83**: 66–76.
4. Bolton CF, Young GB, Zochodne DW. The neurologic complications of sepsis. *Annals of Neurology* 1993; **33**: 94–100.
5. Srung CL, Peduzzi PN, Satney CH, Schein RMH, Wilson MF, Sheagren JN, Hinshaw LB. The Veterans Administration Systemic Sepsis Group. Impact of encephalopathy on mortality in sepsis. *Critical Care Medicine* 1990; **18**: 801–806.
6. Matta BF, Lam AM, Strebel S, Mayberg TS. Cerebral pressure autoregulation and CO_2-reactivity during propofol-induced EEG suppression. *British Journal of Anaesthesia* 1995; **74**: 159–163.
7. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. *Stroke* 1989; **20**: 45–52.
8. Forster A, Juge O, Morel A. Effects of midazolam on cerebral hemodynamics and cerebral vasomotor responsiveness to carbon dioxide. *Journal of Cerebral Blood Flow and Metabolism* 1983; **3**: 246–249.
9. Milde LN, Milde JH, Gallaher WL. Cerebral effects of fentanyl in dogs. *British Journal of Anaesthesia* 1989; **63**: 710–715.
10. Kirkham FJ, Padayachee TS, Parsons S, Seargent LS, House FR, Gosling RG. Transcranial measurements of blood flow velocities in the basal arteries using pulse Doppler ultrasound: Velocity as an index of flow. *Ultrasound in Medicine and Biology* 1986; **12**: 15–21.
11. Bishop CCR, Powell S, Rutt D, Brouse NI. Transcranial Doppler measurement of the middle cerebral flow velocity: A validation study. *Stroke* 1986; **17**: 913–915.
12. Giller CA, Bowman G, Dyer H, Mootz L, Krippner W. Cerebral arterial diameters during changes in blood pressure and carbon dioxide during craniotomy. *Neurosurgery* 1993; **32**: 737–741.
13. Newell WD, Aaslid R, Lam AM, Mayberg TS, Winn HR. Comparison of flow and velocity during dynamic autoregulation testing in humans. *Stroke* 1994; **25**: 793–797.
14. Huber P, Handa J. Effects of contrast material, hypercapnia, hyperventilation, hypertonic glucose and papaverine on the diameter of the cerebral arteries—angiographic determination in man. *Investigational Radiology* 1967; **2**: 17–32.
15. Matta BF, Lam AM. Isoflurane and desflurane do not dilate the middle cerebral artery appreciably. *British Journal of Anaesthesia* 1995; **74**: 486P–487P.
16. Matta BF, Mayberg TS, Lam AM. Direct cerebrovasodilatory effects of halothane, isoflurane and desflurane during propofol-induced isoelectric encephalogram in humans. *Anesthesiology* 1995; **83**: 980–985.
17. Aaslid R. Transcranial Doppler examination techniques. In: Aaslid R, ed. *Transcranial Doppler Sonography*. New York: Springer-Verlag, 1986; 39–59.
18. Strebel S, Kaufmann M, Guardiola PM, Schaefer HG. Cerebral vasomotor responsiveness to carbon dioxide is preserved during propofol and midazolam anesthesia in humans. *Anesthesia and Analgesia* 1994; **78**: 884–888.
19. Eng C, Lam AM, Mayberg TS, Lee C, Mathisen T. The influence of propofol with and without nitrous oxide on cerebral blood flow velocity and CO_2 reactivity in humans. *Anesthesiology* 1992; **77**: 872–879.
20. Aaslid R, Huber P, Nornes H. Evaluation of cerebrovascular spasm with transcranial Doppler ultrasound. *Journal of Neurosurgery* 1984; **60**: 37–42.
21. Bowton DL, Bretels NH, Prough DS, Stump DA. Cerebral blood flow is reduced in patients with sepsis. *Critical Care Medicine* 1989; **17**: 399–403.
22. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. *Stroke* 1989; **20**: 45–52.
23. Tiecks FP, Lam AM, Matta BF, Newell DW. Comparison of static and dynamic methods to evaluate impaired cerebral autoregulation. *Stroke* 1995; **26**: 724.
24. Young GB, Bolton CF, Archibauld YM, Austin TW, Wells GA. The encephalogram in sepsis-associated encephalopathy. *Journal of Clinical Neurophysiology* 1992; **9**: 145–152.
25. Young GB, Bolton CF, Austin TW, Archibauld YM, Gonder J, Wells GA. The encephalopathy associated with septic illness. *Clinical and Investigative Medicine* 1990; **13**: 297–304.
26. Bone RC. Sepsis, the sepsis syndrome, multiorgan failure: a plea for comparable definitions. *Annals of Internal Medicine* 1991; **114**: 332–333.
27. Jeppsson B, Freund HR, Gimmon Z, James JH, Vonmeyenfeldt MF, Fischer JE. Blood brain barrier de-

rangement in sepsis: cause of septic encephalopathy? *American Journal of Surgery* 1981; **141**: 136–141.

28. du Molin GC, Paterson D, Hedley-White J, Broitman SA. *E. coli* peritonitis and bacteraemia cause increased blood–brain barrier permeability. *Brain Research* 1985; **340**: 261–268.
29. Kruger JM, Walter C, Dinarello CA. Sleep-promoting effects of endogenous pyrogen (interluken-1). *American Journal of Physiology* 1984; **246**: R994–R999.
30. Yaghi A, Paterson NAM, McCormack DG. Vascular reactivity in sepsis—importance of controls and role of nitric oxide. *American Journal of Respiratory and Critical Care* 1995; **151**: 706–712.
31. Robert R, Chapelain B, Neliat G. Different effects of interleukin-1 on reactivity of arterial vessels isolated from various vascular beds in the rabbit. *Circulatory Shock* 1993; **40**: 139–143.

British Journal of Anaesthesia 1996; **76**: 795–801

Remifentanil reduces auditory and somatosensory evoked responses during isoflurane anaesthesia in a dose-dependent manner

I. Crabb, C. Thornton, K. M. Konieczko, A. Chan, R. Aquilina, N. Frazer, C. J. Doré and D. E. F. Newton

Summary

We studied 60 patients during stable isoflurane anaesthesia (0.4 MAC) after premedication with temazepam. Patients were allocated randomly to one of three dose regimens of remifentanil: 1 μg kg^{-1} i.v. over 1 min and an infusion of 0.2 μg kg^{-1} min^{-1} (low dose); 2.5 μg kg^{-1} and 0.5 μg kg^{-1} min^{-1} (medium dose); and 5 μg kg^{-1} and 1 μg kg^{-1} min^{-1} (high dose). The auditory (AER) and median nerve somatosensory (SER) responses were elicited throughout, and recorded before and after tracheal intubation, and surgical incision, together with systolic and diastolic arterial pressure and heart rate. Venous blood concentrations of remifentanil were measured at the above times. After administration of remifentanil, Pa and Nb amplitudes of the AER increased at the low dose, remained constant at the medium dose and decreased at the high dose. This dose-related effect was linear and significant ($P = 0.012$, $P = 0.05$). Pa amplitude correlated inversely with remifentanil blood concentrations before and after intubation and incision ($P = 0.002$, $P < 0.001$, $P < 0.001$ and $P < 0.001$). In the SER, P15–N20 amplitudes decreased after administration of remifentanil ($P < 0.001$), whereas P25–N35 and N35–P45 amplitudes increased at all dose concentrations ($P < 0.001$ and $P < 0.001$). After intubation, P15–N20 and N35–P45 amplitudes increased at the low dose, did not change at the medium dose and decreased at the high dose ($P = 0.001$, $P = 0.027$). After remifentanil, systolic and diastolic arterial pressure and heart rate decreased in a linearly dose-related manner ($P = 0.033$, $P < 0.001$, $P < 0.001$). At all doses the three variables increased after intubation ($P = 0.001$, $P < 0.001$, $P < 0.01$), and systolic and diastolic arterial pressure increased after incision ($P = 0.027$, $P = 0.039$). (*Br. J. Anaesth.* 1996; **76**: 795–801)

Key words

Anaesthetics volatile, isoflurane. Analgesics opioids, remifentanil. Monitoring, evoked potentials. Brain, evoked potentials.

Opioids supplement volatile anaesthetics [1, 2] and attenuate the stress response. In high doses they allow anaesthetics doses so low that cardiovascular effects are negligible. Respiratory depressant effects persist into the postoperative period, limiting the technique to major surgery where postoperative ventilation of the lungs is appropriate. The technique could be extended to routine surgery if a very short-acting drug were available. Remifentanil (GI 87084B), a new synthetic phenyl-piperidine opioid has a very rapid onset and a short duration of action because it is metabolized in both blood and tissues by ester hydrolysis. Its pharmacokinetic profile in volunteers and patients undergoing elective in-patient surgery has been described recently [3–6]. Titration of an infusion of remifentanil to produce a desired effect should be possible, making it attractive for use in anaesthesia.

We believe that evoked responses can separate the analgesic and hypnotic components of an anaesthetic. Changes in the early cortical waves of the auditory evoked response (AER) have been shown to be related to the degree of hypnosis with general anaesthetics [7, 8], and changes in the somatosensory evoked response (SER) waves that originate in the region of the thalamus [9, 10] have been shown to reflect the action of analgesic drugs during general anaesthesia [7, 11, 12].

We have examined the effects of three doses of remifentanil on the AER and SER recorded simultaneously during isoflurane anaesthesia. A clinically relevant nociceptive input was provided by tracheal intubation and surgical incision. This enables both testing of the direct effect of the drug during anaesthesia and its possible attenuation of arousal by stimuli.

Patients and methods

After obtaining approval from the local Ethics Committee and informed consent, we studied 60 patients, ASA I or II, undergoing elective surgery. We examined the effect of three regimens of remifentanil, administered in a random, double-blind manner during isoflurane anaesthesia. The

---

I. Crabb, frca, C. Thornton, phd, K. M. Konieczko, frca, A. Chan, frca, R. Aquilina, frca, N. Frazer*, frca, C. J. Doré, bsc, D. E. F. Newton, frca, Department of Anaesthesia, Northwick Park Hospital, Academic Department of Anaesthesia, St Mary's Hospital Medical School, and Northwick Park Institute for Medical Research, Northwick Park Hospital, Watford Road, Harrow HA1 3UJ. Accepted for publication: January 12, 1996.

*Present address: Glaxo Research Inc., 5 Moore Drive, Research Triangle Park, Durham, NC, USA.

Correspondence to D.E.F.N.

Table 1 Measurement times

		AER	SER	Remifentanil blood concn	Haemodynamics
Baseline 1	Immediately before baseline—no remifentanil	✓			
Baseline 2	Immediately before bolus—no remifentanil	✓	✓		✓
Post-bolus	Within 3 min of remifentanil bolus				✓
Pre-intubation	Steady state remifentanil, no stimulus	✓	✓	✓	✓
Post-intubation	Immediately after intubation	✓	✓	✓	✓
Pre-incision	Before incision	✓	✓	✓	✓
Post-incision	Immediately after incision	✓	✓	✓	✓

doses were: a bolus of remifentanil 1 μg kg^{-1} administered over 1 min followed immediately by an infusion of 0.2 μg kg^{-1} min^{-1} (low dose); a bolus of remifentanil 2.5 μg kg^{-1} followed by an infusion of 0.5 μg kg^{-1} min^{-1} (medium dose); and remifentanil 5 μg kg^{-1} bolus followed by an infusion of 1 μg kg^{-1} min^{-1} (high dose).

Premedication comprised oral temazepam 10–20 mg, approximately 1 h before anaesthesia which was induced with propofol 2–2.5 mg kg^{-1}, and a laryngeal mask airway was inserted when consciousness had been lost. Vecuronium 0.1 mg kg^{-1} was given, and paralysis was maintained with an infusion of vecuronium adjusted to allow a single response to the train-of-four stimulus. Patients' lungs were ventilated to achieve an end-tidal carbon dioxide concentration of 4.5–5 %, and anaesthesia was maintained with 0.4 % isoflurane (end-expiratory) in oxygen (measured using a calibrated Datex Ultima). When the end-tidal concentration of isoflurane was stable, typically 10–15 min after induction, glycopyrronium 0.6 mg was given followed 3 min later by remifentanil according to the study design. Ephedrine 10 mg was used when a reduction in arterial pressure was considered to require intervention. Nine minutes after the remifentanil bolus, the laryngeal mask airway was removed and the patient's trachea intubated. Surgical incision occurred at least 10 min after tracheal intubation. The study ended 10 min after incision, the remifentanil infusion was discontinued and nitrous oxide was introduced into the anaesthetic gas mixture.

EVOKED POTENTIALS

Recordings of the AER were started before induction of anaesthesia in all patients. The SER was recorded when consciousness had been lost. Responses were recorded continuously throughout the study. The auditory stimulus was a rarefaction click delivered to both ears simultaneously via close-fitting earpieces. It was presented at 75 dB above the average hearing threshold at a repetition rate of 6 s^{-1}. The somatosensory stimulus of the median nerve at the wrist was a 150-μs electrical pulse produced by a modified Duostim nerve stimulator fitted with an optically isolated trigger from the evoked responses apparatus. It was presented at a rate of 2.2 s^{-1}. The intensity was adjusted to just above the motor threshold before vecuronium was given.

The EEG was recorded for the AER using adhesive silver–silver chloride electrodes on the forehead and left mastoid, and for the SER silver–silver chloride cup electrodes attached with collodion glue at Fz and C3′ (20 mm back from C3) using the standard EEG 10-20 system. The EEG signal was analogue filtered on input with bandwidths of 25–500 Hz for the AER and 10–500 Hz for the SER. The evoked responses were displayed on two interlinked portable PCs using purpose-designed software, and the signals stored on the hard disks of these computers. After each study, the stored information was transferred onto optical disks and analysed off-line. During analysis additional digital filtering was used; a high pass filter of 20 Hz and three-point smoothing for the AER and a high pass filter of 20 Hz for the SER.

The evoked responses were averaged over a period of 2.8 min at steady state before administration of remifentanil and before and after intubation and surgical incision. From the AER, the latency and amplitude of the early cortical waves Pa and Nb were analysed. Latency is measured in milliseconds from time zero (the click). Amplitude is measured in μV as the vertical distance from a peak to a line joining two adjacent troughs, or vice versa. An index of the AER generated automatically from the mean second differential of the waveform at 30–60 ms was also recorded (the second differential gives a value which increases both with amplitude and with the number of peaks occurring in the window). The SER was analysed with respect to latency of the waves P15, N20, P25, N35 and P45, and the amplitude of P15–N20, N20–P25, P25–N35 and N35–P45. The amplitudes were measured as the vertical distance (μV) between successive waves.

Arterial pressure and heart rate were recorded every 3 min using a Dinamap, and throughout the procedure an ECG and pulse oximeter were attached to the patient.

REMIFENTANIL BLOOD CONCENTRATIONS

Venous blood samples were obtained in lithium heparin tubes from the contralateral arm for analysis of concentrations of remifentanil immediately before, and 3 min after intubation and correspondingly before and after surgical incision. Some of this sample (5 ml) was mixed with 20 μl of 50 % citric acid and vortexed for 10 s. Aliquots of 2.5 ml were then stored at −20 °C until analysis. Remifentanil analysis was carried out by Glaxo Inc. using the method of Selinger, Lanzo and Sekut [13]. The assay had a lower limit of resolution of 0.1 ng ml^{-1} and a coefficient of variation of < 11.5 %.

STATISTICAL ANALYSIS

Measurements of the following variables were made at the times shown in table 1. AER, SER and haemodynamic data were normalized by $\log_{10}$ transformation and analysis of variance was performed. Between-subject comparisons were made for the effects of dose, and within-subject comparisons for the effects of remifentanil infusion, intubation and incision. Regressions of the above variables and $\log_{10}$ transformed remifentanil blood concentrations were also carried out. All calculations were performed using Genstat 5 release 3.2 (IBM PC 3086/DOS).

Results

The relationship between blood concentrations and infusion rates is illustrated in figure 1. Concentrations increased slightly with time in all groups.

AUDITORY EVOKED RESPONSE

The effect of remifentanil on the AER is illustrated in figure 2 by group changes in Pa amplitude from baseline 1 to after incision. The three groups (low-, medium- and high-dose) showed similar values for baseline 1 and baseline 2 (fig. 2, table 2). There was a significant increase in all three groups between baseline 1 and 2 ($P = 0.024$). Comparing baseline 2 with the next period (before intubation), when the infusion of remifentanil was in progress, Pa amplitude increased at the low dose of remifentanil, remained constant at the medium dose and decreased at the high dose. This dose-related effect was linear and statistically significant ($P = 0.012$). Similar changes were seen in the AER index ($P = 0.001$) and Nb amplitude ($P = 0.05$).

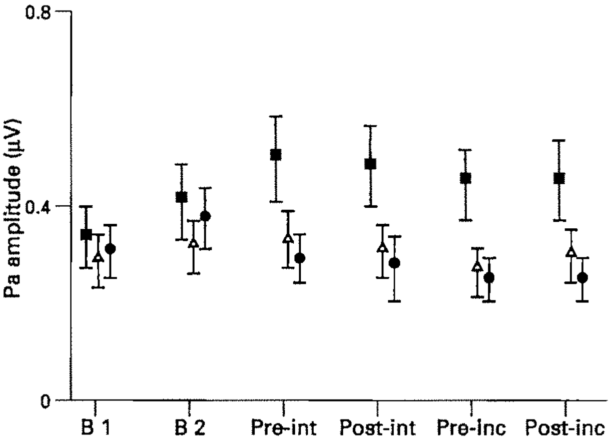


Figure 2 Pa amplitude (mean, 95 % confidence limits), 5 min (baseline 1 (B1)) and immediately before administration of remifentanil (baseline 2 (B2)), before (Pre-int) and after (Post-int) tracheal intubation and before (Pre-inc) and after (Post-inc) incision at the low- (■), medium- (△) and high- (●) dose regimens.

The differences in Pa amplitude between the three groups during administration of remifentanil were maintained throughout the study. There were no statistically significant differences caused by intubation or incision for any of the AER variables. The AER index and Nb amplitude (table 2) showed similar changes to Pa amplitude, which was not unexpected as they are related variables. The changes in these variables from baseline 1 to baseline 2 showed similar trends as Pa amplitude, but these were not significant. The changes with infusion rate were borne out when the AER data were plotted against blood concentrations of remifentanil. For example, there were statistically significant decreases in Pa amplitude (fig. 3) when individual values before and after intubation and before and after incision were plotted against blood concentration ($P = 0.002$, $P < 0.001$, $P < 0.001$ and $P < 0.001$, respectively).

SOMATOSENSORY EVOKED RESPONSE

The earlier wave P15–N20 and N20–P25 amplitudes (table 3) decreased with administration of remifentanil (baseline 2 to before intubation) at all dose

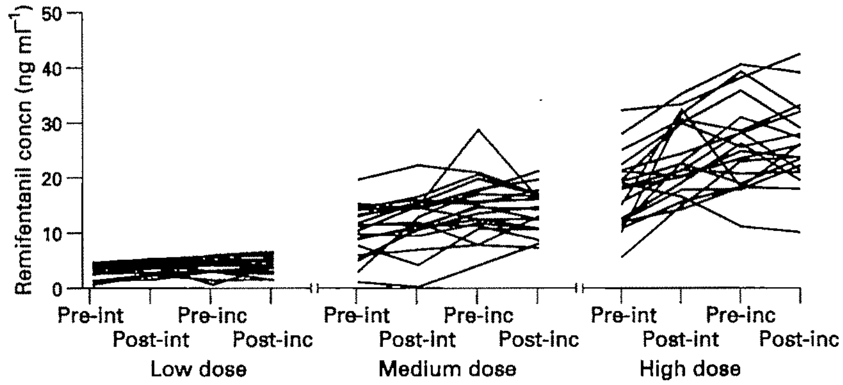


Figure 1 Blood concentrations of remifentanil at the three infusion regimens: remifentanil 1 μg kg^{-1} and infusion of 0.2 μg kg^{-1} min^{-1} (low dose); remifentanil 2.5 μg kg^{-1} and infusion of 0.5 μg kg^{-1} min^{-1} (medium dose); remifentanil 5 μg kg^{-1} and infusion of 1 μg kg^{-1} min^{-1} (high dose). Pre-int = before intubation; Post-int = after intubation; Pre-inc = before incision; Post-inc = after incision.

Table 2 Auditory evoked response. Group geometric means (95 % confidence limits) for low, medium and high doses of remifentanil. Significance levels are referred to in the text

Dose	Baseline 1	Baseline 2	Pre-intubation	Post-intubation	Pre-incision	Post-incision
Pa amplitude (μV)						
Low	0.34 (0.28–0.41)	0.42 (0.35–0.51)	0.51 (0.43–0.61)	0.49 (0.41–0.58)	0.46 (0.38–0.55)	0.46 (0.38–0.55)
Medium	0.29 (0.24–0.35)	0.32 (0.27–0.38)	0.33 (0.27–0.39)	0.31 (0.26–0.37)	0.27 (0.23–0.33)	0.30 (0.25–0.36)
High	0.31 (0.26–0.37)	0.38 (0.32–0.45)	0.29 (0.24–0.34)	0.28 (0.24–0.34)	0.25 (0.21–0.30)	0.25 (0.21–0.30)
Nb amplitude (μV)						
Low	0.27 (0.22–0.33)	0.32 (0.26–0.39)	0.41 (0.33–0.50)	0.39 (0.32–0.48)	0.38 (0.32–0.47)	0.35 (0.29–0.43)
Medium	0.27 (0.22–0.33)	0.25 (0.21–0.31)	0.24 (0.19–0.29)	0.22 (0.18–0.27)	0.22 (0.18–0.28)	0.26 (0.21–0.32)
High	0.26 (0.21–0.31)	0.29 (0.24–0.35)	0.25 (0.20–0.30)	0.21 (0.17–0.26)	0.23 (0.19–0.28)	0.21 (0.17–0.25)
AER index						
Low	13.3 (11.4–15.6)	15.5 (13.3–18.2)	17.7 (15.1–20.7)	18.4 (15.8–21.5)	14.3 (12.3–16.7)	15.7 (13.5–18.4)
Medium	12.4 (10.6–14.5)	13.8 (11.8–16.1)	11.6 (10.0–13.6)	12.6 (10.8–14.7)	10.0 (8.5–11.8)	10.8 (9.2–12.7)
High	15.2 (13.0–17.8)	15.4 (13.2–18.0)	10.4 (8.9–12.2)	11.5 (9.9–13.5)	9.7 (8.3–11.3)	9.6 (8.2–11.2)

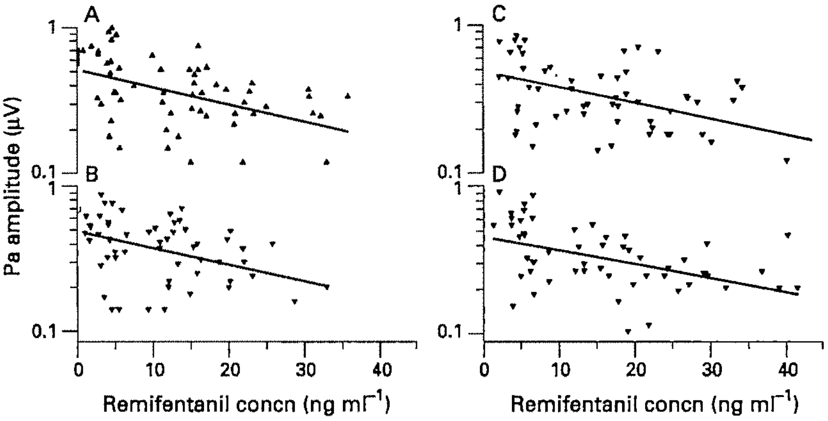


Figure 3 Pa amplitude *vs* measured blood concentrations of remifentanil before (B) and after (A) intubation and before (D) and after (C) incision.

Table 3 Somatosensory evoked response. Group geometric means (95 % confidence limits) for low, medium and high doses of remifentanil

Dose	Baseline 2	Pre-intubation	Post-intubation	Pre-incision	Post-incision
P15–N20 amp. (μV)					
Low	1.7 (1.5–1.8)	1.2 (1.1–1.4)	1.4 (1.3–1.6)	1.2 (1.1–1.3)	1.2 (1.1–1.3)
Medium	2.3 (2.1–2.5)	1.8 (1.6–1.9)	1.8 (1.6–2.0)	1.4 (1.3–1.6)	1.3 (1.2–1.5)
High	2.2 (2.0–2.4)	1.8 (1.6–1.9)	1.5 (1.3–1.6)	1.1 (1.0–1.2)	1.2 (1.0–1.3)
N20–P25 amp. (μV)					
Low	3.2 (2.9–3.6)	3.0 (2.7–3.4)	3.3 (3.0–3.7)	2.6 (2.3–2.9)	2.7 (2.4–3.0)
Medium	3.9 (3.5–4.3)	3.7 (3.3–4.1)	3.4 (3.1–3.9)	2.8 (2.5–3.2)	2.7 (2.4–3.0)
High	4.1 (3.7–4.6)	3.7 (3.3–4.2)	3.8 (3.4–4.2)	2.6 (2.4–2.9)	2.8 (2.5–3.1)
P25–N35 amp. (μV)					
Low	2.7 (2.4–3.1)	3.4 (3.0–3.9)	3.7 (3.2–4.2)	3.0 (2.6–3.4)	3.2 (2.8–3.7)
Medium	2.8 (2.4–3.2)	3.5 (3.1–4.0)	3.5 (3.1–4.0)	3.2 (2.8–3.7)	3.4 (2.9–3.9)
High	3.0 (2.6–3.5)	3.8 (3.3–4.4)	3.8 (3.3–4.3)	3.0 (2.6–3.5)	3.2 (2.8–3.7)
N35–P45 amp. (μV)					
Low	1.8 (1.5–2.0)	2.0 (1.7–2.3)	2.2 (1.9–2.6)	2.4 (2.1–2.8)	2.5 (2.2–2.9)
Medium	1.3 (1.1–1.5)	1.9 (1.6–2.2)	1.9 (1.7–2.2)	2.1 (1.8–2.4)	2.1 (1.8–2.4)
High	1.7 (1.5–2.0)	2.3 (2.0–2.6)	1.8 (1.6–2.1)	2.1 (1.8–2.4)	2.1 (1.8–2.4)

concentrations. This was significant for P15–N20 ($P < 0.001$) but not for N20–P25. In contrast, the later wave (P25–N35 and N35–P45) amplitudes increased significantly at all dose concentrations of remifentanil ($P < 0.001$ and $P < 0.001$, respectively). None of these changes was dose related.

There were significant linear dose-related changes in P15–N20 and N35–P45 amplitudes after intubation ($P = 0.001$, $P = 0.027$). The amplitudes increased in the low-dose group, were virtually changed in the medium-dose group and decreased in the high-dose group. This is in contrast with the AER variables where no such linear dose-related trends with intubation were observed. Figure 4 shows the differences before and after intubation for P15–N20 amplitude of the SER and Pa amplitude of the AER.

The SER observations were borne out in the

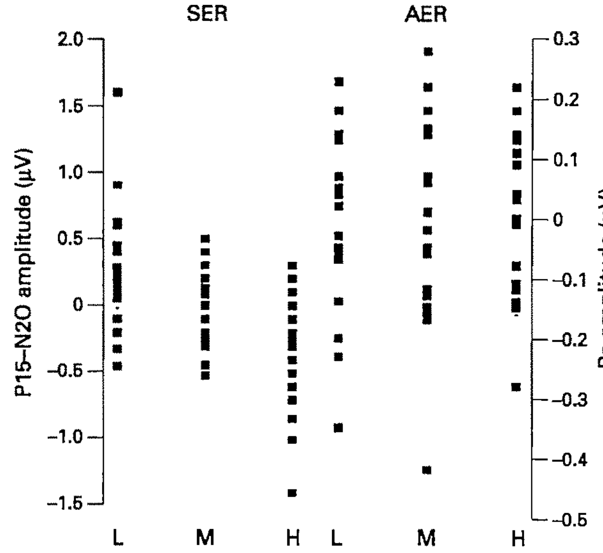


Figure 4 Change in somatosensory (SER) and auditory (AER) evoked potentials (P15–N20 amplitude and Pa amplitude) after tracheal intubation. There is a dose-related change in the SER response, and no change in the AER related to dose. L = low, M = medium, H = high dose.

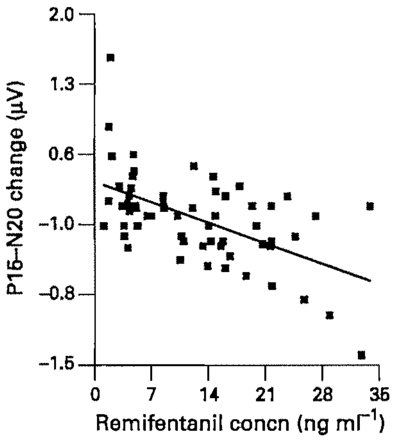


Figure 5 Change in the P15–N20 somatosensory response after tracheal intubation *vs* mean blood concentrations of remifentanil before and after intubation ($P < 0.001$).

relationship with blood concentrations (fig. 5). There were no significant relationships between any of the SER variables, before and after intubation and before and after incision, and remifentanil blood concentration, but there were significant relationships between the differences in P15 and P25 latencies before and after intubation which increased ($P < 0.001$ and $P = 0.04$), and P15–N20 (fig. 5) and N35–P45 amplitudes which decreased ($P < 0.001$ and $P = 0.04$), with increasing blood concentrations of remifentanil.

As with the AER variables there were no significant effects of incision on any of the somatosensory evoked response amplitudes.

HAEMODYNAMIC DATA

The haemodynamic effects of remifentanil are shown in table 4. After bolus administration of remifentanil, all three variables (systolic and diastolic arterial pressures and heart rate) decreased significantly in a linearly dose-related manner ($P = 0.033$, $P < 0.001$, $P < 0.001$, respectively).

Two patients in the high-dose group were given ephedrine to supplement fluids in maintaining arterial pressure within the clinical range 15 and 6 min after the bolus of remifentanil. The first of these and another different patient were given ephedrine after incision for the same reason.

Table 4 Haemodynamic variables. Group geometric means (95 % confidence limits) for low, medium and high doses of remifentanil

Dose	Baseline 2	Post-bolus	Pre-intubation	Post-intubation	Pre-incision	Post-incision
Systolic AP (mm Hg)						
Low	112 (108–117)	95 (92–99)	100 (96–104)	106 (102–111)	103 (99–107)	108 (104–112)
Medium	113 (109–118)	94 (91–98)	98 (94–102)	103 (99–108)	97 (93–101)	100 (96–104)
High	120 (115–125)	93 (90–97)	98 (94–102)	103 (99–107)	96 (92–100)	100 (96–104)
Diastolic AP (mm Hg)						
Low	62 (59–66)	50 (48–53)	51 (48–54)	57 (54–60)	52 (49–55)	57 (54–60)
Medium	67 (63–70)	51 (49–54)	55 (52–58)	57 (54–60)	55 (52–58)	55 (52–58)
High	68 (65–72)	46 (44–49)	49 (47–52)	55 (52–58)	52 (50–55)	55 (52–58)
Heart rate (beat min^{-1})						
Low	87 (83–90)	81 (78–84)	80 (77–83)	85 (81–88)	79 (76–83)	79 (76–82)
Medium	78 (75–81)	68 (66–71)	69 (66–72)	71 (69–74)	66 (63–69)	66 (63–69)
High	83 (80–86)	66 (63–68)	67 (64–69)	69 (66–72)	65 (63–68)	65 (62–67)

At the three dose concentrations of remifentanil, systolic and diastolic arterial pressures and heart rate increased significantly after intubation ($P = 0.001$, $P < 0.001$, $P < 0.01$, respectively), and systolic and diastolic arterial pressures increased significantly after incision ($P = 0.027$, $P = 0.039$). These changes occurred at all doses and were also reflected in the relationship with blood concentrations. Diastolic and systolic arterial pressures after intubation were inversely related to remifentanil blood concentrations ($P = 0.002$ and $P = 0.001$, respectively). Heart rate before intubation was significantly inversely related to blood concentrations of remifentanil ($P < 0.001$).

Discussion

As venous blood concentrations of remifentanil increased steadily with time at all dose concentrations (fig. 1), steady state was not reached during the study, and concentrations within a dose group were variable at each measurement time. The higher variability of pre-intubation concentrations and their lower mean values compared with subsequent measurements demonstrate that the loading bolus doses were not large enough. In a pilot study, greater bolus doses had produced unacceptable hypotension. We have presented the results in relation to dose, and measured blood concentrations, because it is not yet clear which has the closest relationship to the pharmacodynamic response. In this study there was no real difference in the results between dose and blood concentration. Although none of the doses used was able to completely suppress the cardiovascular effects of stimuli, the changes in cardiovascular variables were small and not clinically significant (table 4).

Studies which have compared remifentanil with alfentanil have reported greater haemodynamic stability with remifentanil, irrespective of the dose rate [6, 14]. In both of these studies the haemodynamic changes were also small. In one [6], the remifentanil infusion rate was increased before strong stimulation, which demonstrates that the short half-life of remifentanil [15] may allow greater control of haemodynamic state. The extent to which these doses are effective remains to be seen when the drug is studied in patients with greater cardiovascular instability.

As studies by other workers [16–18] have demonstrated little or no effect of opioids on the AER, we were surprised to see a dose-dependent effect on the AER variables. This would not have been detected with only one dose. In patients receiving the low dose, AER amplitudes increased. It is likely that this was the continuation of a trend which was occurring throughout the baseline period (see fig. 2) reaching a maximum at the pre-intubation measurement. The later SER wave amplitudes P25–N35 and N35–P45 (table 3) also increased after bolus administration of remifentanil, unlike the earlier waves P15–N20 and N20–P25 which decreased. One explanation for these observations is a decrease in depth of anaesthesia caused by factors such as reducing blood concentration of propofol, discomfort of the laryngeal mask and arterial pressure cuff. Until the pre-intubation measurement, the changes in Pa amplitude in the three patients groups were not significantly different from each other. From the post-intubation measurement onwards, the low dose of remifentanil arrested the trend, and the medium and high doses reversed it, resulting in the linear dose-dependent relationship.

The SER waves did not show a dose-dependent relationship. Previously, we observed later cortical SER waves behaving differently from the earlier pontine thalamic waves and in a similar manner to the cortical AER when we compared the effects of isoflurane and nitrous oxide [7]. We found that nitrous oxide decreased the amplitudes of the earlier complexes P15–N20 and N20–P25 more than isoflurane, suggesting that these subcortical waves may reflect analgesia. In contrast, isoflurane decreased the amplitudes of the later waves P25–N35 and N35–P45. The findings of this study support the suggestion that cortical waves reflect the hypnotic component of anaesthesia. Freye, Buhl and Ciaramelli [12] showed a dose-related decrease in the amplitude of N20 in response to alfentanil, and also that this response was related to the action of mu opioids, whereas opioids with a strong kappa activity affected the cortical SER waves.

This study was designed to demonstrate the effect of remifentanil on the changes in the evoked responses to strong stimuli which have been reported previously by us and others [8, 19, 20]. On this occasion both tracheal intubation and incision were included. There was no change in the AER variables in response to either stimulus (fig. 2). It would have been more impressive to show a graded attenuation of the effect of stimulation on the AER amplitudes such as was seen in the changes in SER amplitudes (fig. 4, table 3). Inclusion of a "no remifentanil" control or lower dose ranges of remifentanil had been contemplated but rejected because of the risk of awareness in patients undergoing tracheal intubation and incision receiving only 0.4% isoflurane after temazepam and propofol, and with no analgesic. In early experiences with a new drug, choice of dose range is a notoriously difficult decision and we were not prepared to give less than the low dose described here. In the light of our findings, future studies using the same background anaesthesia and lower remifentanil doses could perhaps be considered.

The SER showed a response to intubation but the AER did not. Sebel and colleagues [21] have previously reported a similar SER response to intubation in patients during thiopentone and nitrous oxide anaesthesia, and after administration of fentanyl a response to surgical incision. The mechanism of the response to one stimulus (the median nerve SER) being enhanced by another unrelated stimulus (surgery or intubation) requires explanation. One possibility is a local increase in available neurotransmitters in response to a large nociceptive insult. Another possibility is an effect regulated through the mechanism of CNS arousal. This effect is blocked by increasing concentrations of opioid. While the lowest dose of opioid was insufficient to inhibit the SER, no responses were seen in the AER.

The dose-dependent depressant effects of remifentanil on the early cortical AER in the unstimulated patient have yet to be explained. There are three possibilities: first that remifentanil has an interaction with isoflurane—a combined effect on the cortex; second, that deafferentation, that is a general dampening down of incoming stimulation, produces cortical depression; and third, that mu opioids may have a direct depressive effect on the cortex.

Acknowledgement

This study was supported in part by Glaxo Research and Development Ltd.

References

1. Murphy MR, Hug CC. The enflurane sparing effect of morphine, butorphenol and nalbuphine. *Anesthesiology* 1982; **57**: 489–492.
2. Murphy MR, Hug CC. The anesthetic potency of fentanyl in terms of its reduction of enflurane MAC. *Anesthesiology* 1982; **57**: 485–488.
3. Rosow C. Remifentanil: A unique opioid analgesic. *Anesthesiology* 1993; **79**: 875–876.
4. Glass PSA, Hardman D, Kamiyama Y, Quill TJ, Marton G, Grosse CM, Hermann D. Preliminary pharmacokinetics and pharmacodynamics of an ultrashort acting opioid: Remifentanil (GI87084B). *Anesthesia and Analgesia* 1993; **77**: 1031–1040.
5. Egan TD, Lemmens HJM, Fiset P, Hermann DJ, Muir KT, Stanski DR, Schafer SL. The pharmacokinetics of the new short-acting opioid remifentanil (GI87084) in healthy volunteers. *Anesthesiology* 1993; **79**: 881–892.
6. Monk TG, Batenhorst RL, Folger WH, Kirkham AJT, Lemon DJ, Martin KJ, Venker DC. A comparison of remifentanil and alfentanil during nitrous–narcotic anesthesia. *Anesthesia and Analgesia* 1994; **78**: S293.
7. Thornton C, Creagh-Barry P, Jordan C, Luff NP, Doré CJ, Henley M, Newton DEF. Somatosensory and auditory evoked responses recorded simultaneously: differential effects of nitrous oxide and isoflurane. *British Journal of Anaesthesia* 1992; **68**: 508–514.
8. Thornton C, Creagh-Barry P, Jordan C, Newton DEF. Anaesthetic depth and auditory evoked potentials. *Acta Anaesthesiologica Scandinavica* 1993; 37(Suppl. 100): 105–108.
9. Abbruzzesse M, Favale E, Leandri M, Ratto S. New subcortical components of the cerebral somatosensory evoked potential in man. *Acta Neurologica Scandinavica* 1978; **58**: 325–332.
10. Chiappa KH. Short latency somatosensory evoked responses: interpretation. In: Chiappa KH, ed. *Evoked Potentials in Clinical Medicine*. New York: Raven Press, 1985; 251–324.
11. Freye E, Buhl RW. Somatosensory evoked potentials for the evaluation of analgesic properties of nalbuphine in man. *Anesthesia and Analgesia* 1986; **65**: S51.
12. Freye E, Buhl R, Ciaramelli F. Opioids with different affinity for subreceptors induce different effects on early and late sensory evoked potentials (SEP) in man. *National Institute of Drug Research Monograph Service* 1986; **75**: 551–554.
13. Selinger K, Lanzo C, Sekut A. Determination of remifentanil in human and dog blood by HPLC with UV detection. *Journal of Pharmaceutical and Biomedical Analysis* 1994; **12**: 243–248.
14. Kallar SK, Hurt TW, Wetchler BV, Shaw DL, Jamerson B. A single blind comparative study of the safety and efficacy of remifentanil and alfentanil for outpatient anesthesia. *Anesthesiology* 1994; **61**: A32.
15. Westmoreland CL, Hoke JF, Sebel PS, Hug CC, Muir KT. Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. *Anesthesiology* 1993; **79**: 893–903.
16. Schwender D, Keller I, Klasing S, Madler C. Middle-latency auditory evoked potentials during high-dose opioid analgesia. *Anaesthesist* 1990; **39**: 299–305.
17. Schwender D, Rimkus T, Haessler R. Effects of increasing doses of alfentanil, fentanyl, and morphine on mid latency auditory evoked potentials. *British Journal of Anaesthesia* 1993; **71**: 622–628.
18. Schwender D, Weninger E, Daunderer M, Klasing S, Poppel E, Peter K. Anesthesia with increasing doses of sufentanil and midlatency auditory evoked potentials in humans. *Anesthesia and Analgesia* 1995; **80**: 499–505.
19. Thornton C, Konieczko K, Jones JG, Jordan C, Doré CJ, Heneghan CPH. Effect of surgical stimulation on the auditory evoked response. *British Journal of Anaesthesia* 1988; **60**: 372–378.
20. Schwender D, Golling W, Klasing S. Effects of surgical stimulation on midlatency auditory evoked potentials during general anaesthesia with propofol/fentanyl, isoflurane/fentanyl and flunitrazepam/fentanyl. *Anaesthesia* 1994; **49**: 572–578.
21. Sebel PS, Withington PS, Rutherfoord CF, Markham K. The effect of tracheal intubation and surgical stimulation on median nerve somatosensory evoked potentials during anaesthesia. *Anaesthesia* 1988; **43**: 857.

British Journal of Anaesthesia 1996; **76**: 802–805

Effect of the addition of alfentanil to lignocaine during axillary brachial plexus anaesthesia

W. P. GORMLEY, J. M. MURRAY, J. P. H. FEE AND S. BOWER

Summary

Peripheral administration of opioids has been suggested as a means of improving regional block. We studied 60 patients receiving axillary brachial plexus anaesthesia, allocated randomly to receive either normal saline 10 ml or normal saline 10 ml with alfentanil 10 µg/kg body weight through an axillary cannula. All patients received 1.5% lignocaine at a dose of 7 mg/kg body weight with adrenaline 1 in 200000. The incidence of satisfactory block was similar in both groups. Although the percentage of patients with complete anaesthesia in the median nerve distribution was greater in the alfentanil group, there was no significant difference in any other distribution. The time to return of sensation and motor function was prolonged significantly in the alfentanil group ($P <$ 0.05). After return of normal sensation, there was no significant difference between groups in postoperative analgesia. In a second part of the study, there was no significant increase in plasma concentrations of alfentanil in 10 patients given lignocaine and alfentanil, as outlined above. These observations suggest that alfentanil may have a peripheral local anaesthetic action. (*Br. J. Anaesth.* 1996; **76**: 802–805).

Key words

Anaesthetic techniques, regional, brachial plexus. Anaesthetics local, lignocaine. Analgesics opioids, alfentanil.

Traditionally, antinociception has been associated with occupation of opioid receptors exclusively within the spinal cord [1]. Recently, opioid receptors have been discovered on immune cells, sympathetic nerve fibres and peripheral neurones [2, 3]. Animal behavioural studies have demonstrated antinociception after peripheral administration of opioids [4].

Peripheral effects of opioids may improve regional anaesthesia without centrally mediated side effects. This would clearly be of benefit during brachial plexus anaesthesia, a commonly used anaesthetic technique for upper limb surgery. However, clinical studies have shown results ranging from improved quality of anaesthesia and postoperative analgesia [5–7] to no effect [8, 9].

Ineffective opioid activity during brachial plexus anaesthesia may be because of the inability of the opioid to penetrate axonal myelin and the nerve membrane [4]. In this study, alfentanil was chosen as it is highly un-ionized (89%) at pH 7.4 [10]. Lignocaine is a commonly used short-acting local anaesthetic which may benefit from improvement in duration of action or postoperative analgesia.

Patients and methods

After obtaining local Ethics Committee approval and written, informed consent, we studied 60 patients, ASA I and II, aged 18–70 yr, weighing 50–100 kg. All were unpremedicated and undergoing elective upper limb surgery.

An 18-gauge i.v. cannula was inserted into the contralateral arm. Routine monitoring was used throughout the study. After sterile preparation, axillary brachial plexus block was carried out using a 20-gauge cannula, as described by Hill and Campbell [11]. Loss of resistance to saline was used to locate the axillary sheath. Having found the sheath, the needle was removed, the cannula advanced and secured in place. A length of primed plastic tubing was attached to the cannula and to a syringe. The patients were then allocated randomly to one of two groups using a sealed envelope technique. Group A received alfentanil 10 µg/kg body weight made up to 10 ml with 0.9% saline. Group S received 0.9% saline 10 ml. These solutions were prepared before use by a colleague who took no further part in the study. All patients received commercially prepared 1.5% lignocaine with adrenaline 1 in 200000 to a total dose of 7 mg/kg body weight. The pH of the mixed solutions in each group was measured later using a pH meter.

Sensory and motor observations were performed every 10 min for 30 min after injection by an observer who was unaware of the solution used. Anaesthesia was assessed using response to pinprick on a three-point scale: normal, impaired or absent sensation. The extent of motor block was assessed

---

W. P. GORMLEY, MB, CHB, FFARCSI, Department of Anaesthesia, The Ulster Hospital, Dundonald, Belfast BT16 0RH, J. M. MURRAY, MD, FFARCSI, Department of Anaesthesia, The Ulster Hospital, Dundonald, Belfast BT16 0RH and The Queen's University of Belfast, 97 Lisburn Road, Belfast, Northern Ireland. J. P. H. FEE, MD, PHD, FFARCSI, Department of Anaesthesia, The Queen's University of Belfast, 97 Lisburn Road, Belfast, Northern Ireland. S. BOWER, MB, CHB, PHD, University of Newcastle upon Tyne, Newcastle upon Tyne. Accepted for publication: February 13, 1996.

Correspondence to J.M.M.

using hand grip with a modified Bromage scale: normal, impaired or absent motor function [12]. The block was judged overall to be satisfactory if anaesthesia involved at least two peripheral nerve distributions, including one of the following: median, ulnar, radial or musculocutaneous. The use of rescue adjuvants such as nerve blocks, infiltration or sedation was recorded. The return of sensory and motor function and the time to first request for analgesia were noted. A visual analogue pain score was obtained at hourly intervals for 6 h and at 12 and 24 h. Sedation, ventilatory frequency and peripheral oxygen saturation were also noted at these times. Systemic effects such as nausea, vomiting or pruritus were recorded.

In the second part of the study, 10 patients received axillary brachial plexus anaesthesia as described for group A. In addition, 10-ml samples of venous blood were obtained at 30 min, 1, 2, 3 and 4 h after injection. The samples were centrifuged and frozen to −40 °C. Plasma concentrations of alfentanil were measured later by a radioimmunoassay technique of sensitivity 2 pg ml^{-1} and coefficient of variation 7% [13].

Advice regarding statistical analysis was obtained from the Department of Statistics at the Queen's University of Belfast. Patient data and characteristics were compared using unpaired Student's *t* test and Mann–Whitney *U* test as appropriate. Onset times in the peripheral nerve distributions were categorized as 0–10, 10–20, 20–30 and greater than 30 min. The number of patients in each category was calculated for all peripheral nerve distributions and for motor function. They were compared using the chi-square test. The fact that complete anaesthesia failed to develop in certain peripheral nerve distributions precluded the use of analysis of variance. $P < 0.05$ was considered statistically significant.

Results

There were 32 patients in group S and 28 patients in group A. The type of surgery included correction of Dupuytren's contracture (57%), carpel tunnel median nerve decompression (26%) and others (17%). There was no significant difference between groups in age, weight, sex or duration of surgery (table 1).

There was a greater percentage of patients with complete anaesthesia in the median nerve distribution in group A at 30 min after injection ($P <$ 0.05). There was no significant difference between groups in any other peripheral nerve distribution or in motor function (fig. 1).

The overall incidence of satisfactory block was 91.7% and was not significantly different between groups. The use of rescue adjuvants was similar for both groups. The times to return of sensation ($P =$ 0.013) and motor function ($P = 0.001$) were prolonged significantly in group A compared with group S (table 2). The time to first request for analgesia was similar in both groups.

Table 1 Patient data (mean (SD or range) or number)

Group	Age (yr)	Weight (kg)	Sex (M/F)	Duration of surgery (min)
Saline	50.4 (18–69)	72.4 (11.2)	24/8	65.2 (18.7)
Alfentanil	44.1 (20–62)	75.5 (11.8)	20/8	74.6 (33.3)

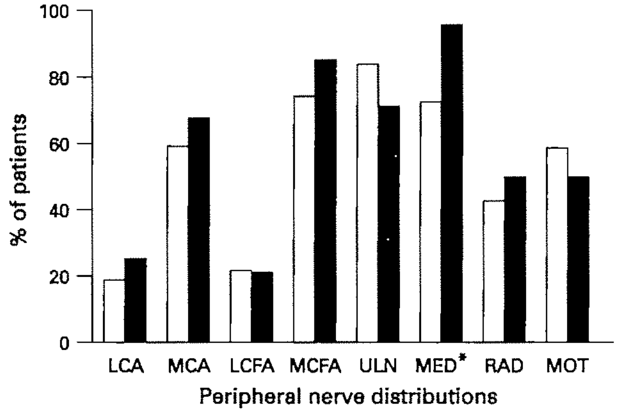


Figure 1 Percentage of patients with complete anaesthesia or motor block 30 min after injection of saline (□) or alfentanil (■). The peripheral distributions shown are the lateral cutaneous nerve of the arm (LCA), median cutaneous nerve of the arm (MCA), lateral cutaneous nerve of the forearm (LCFA), median cutaneous nerve of the forearm (MCFA), ulnar nerve (ULN), median nerve (MED) and radial nerve (RAD). Motor block (MOT) is also shown. $*P < 0.05$.

Table 2 Time to return of sensation and motor function, and time to first request for analgesia (mean (SD) minutes). $*P < 0.05$

Group	Return of sensation	Return of motor function	Time to first analgesia
Saline	189.7 (58)	191.6 (43)	335. 8 (171)
Alfentanil	231.7 (64.8)*	240.6 (61.9)*	320 (92)

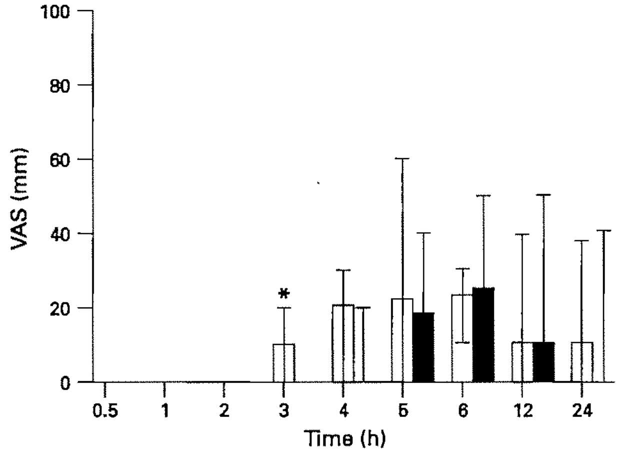


Figure 2 Postoperative visual analogue scores (VAS) in the saline (□) and alfentanil (■) groups (median, interquartile range). $*P < 0.05$.

There was a significant reduction in visual analogue pain scores (VAS) at 3 h in group A ($P =$ 0.019) but not at any other time (fig. 2). There were no significant differences between groups in sedation, peripheral oxygen saturation or ventilatory

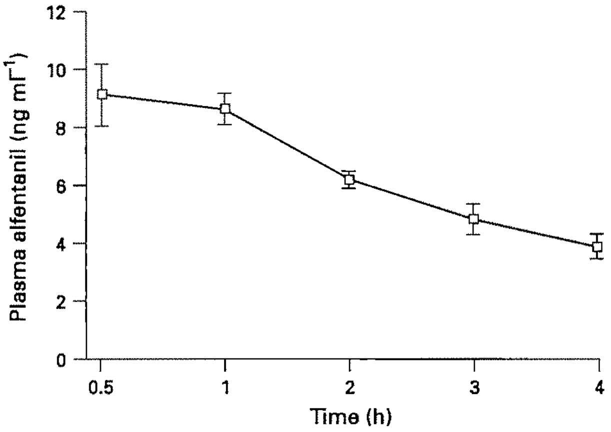


Figure 3 Mean (SEM) plasma concentrations of alfentanil for 10 patients.

frequency. Two patients in group A and one patient in group S developed pruritis. One patient in group A developed nausea.

Plasma concentrations of alfentanil did not increase significantly. Concentrations were greatest at 30 min after injection, with a decrease over the next few hours (fig. 3).

There was no significant difference in the pH of the anaesthetic solution between group S (4.01) and group A (4.08).

Discussion

Currently, there is significant cytochemical and behavioural evidence for the existence of peripheral opioid receptor sites. These have been demonstrated on sympathetic nerve fibres and primary afferent neurones [3]. In addition, endogenous opioids have been detected in peripheral terminals of sensory nerves [14]. Animal behavioural studies demonstrating peripheral antinociception have almost universally used response latency to pain inflicted on an inflamed paw [4].

Buprenorphine and morphine have been shown to improve postoperative analgesia after brachial plexus anaesthesia [5–7]. Faster onset of anaesthesia has been demonstrated in two studies with fentanyl [15, 16]. Other investigators have found no benefit from the addition of morphine or fentanyl [8, 9]. One suggestion for such inconclusive results is that certain opioids may be unable to penetrate layers of myelin [4]. These are particularly numerous on the proximal nerve axons found in the brachial plexus. It was thought that the use of a highly un-ionized opioid such as alfentanil may have facilitated penetration of the nerve sheath. The dose of alfentanil was chosen after a pilot study comparing 0, 5 and 10 µg/kg body weight, in which a clinical effect was demonstrated only with 10 µg kg^{-1}. In order to reduce any physical interaction, the alfentanil and lignocaine solutions were not mixed before injection. However, it is possible that acidic commercially prepared lignocaine and adrenaline solutions may alter the ionic equilibrium of alfentanil within the brachial plexus sheath.

Our study demonstrated improvement in the onset of anaesthesia in one peripheral nerve distribution. Improvement was not seen in any other distribution or in the development of paresis. These findings are therefore unlikely to be clinically important. However, there was a significant prolongation of sensory and motor block. These clinical observations would suggest that alfentanil may have a local anaesthetic action affecting both sensory and motor neurones. We demonstrated that the systemic absorption of alfentanil after injection into to the axillary sheath produces plasma concentrations unlikely to produce clinical effects [17].

Opioid receptors are thought to produce antinociception in a variety of ways. A local anaesthetic action on the excitability of nerve terminals and the propagation of nerve impulses is thought to be brought about by two distinct mechanisms. The first involves an early decrease in sodium conductance and a delayed decrease in potassium conductance [18]. This effect is not reversed by naloxone and has been demonstrated on peripheral mammalian nerves with fentanyl and sufentanil [19, 20]. Impaired nerve impulse conduction is seen only at high concentrations of opioid (greater than fentanyl 50 µg ml^{-1}) [19]. The second local anaesthetic action is reversible by naloxone and involves a decrease in sodium conductance alone [18]. This action occurs at lower opioid concentrations and would appear to relate best to the results of our study. It would have been interesting to observe the effects of naloxone in another group of patients. However, there is uncertainty over which route, how much and over what period naloxone should be administered.

Other mechanisms of action of peripheral opioid receptors involve inhibition of release of substance P from peripheral terminals of primary afferent neurones [21]. This effect is unlikely to have played a significant part in our study. The improvement in visual analogue pain score at 3 h is most likely because of prolonged anaesthesia as no improvement was seen after the return of sensation.

It is known that the peripheral effects of opioids are enhanced after inflammation [22]. This may be because of infiltration of immune cells which would produce a delayed analgesic response. There is evidence for the existence of endogenous opioids in a variety of immune cells infiltrating inflamed subcutaneous tissue [23]. An alternative suggestion is that both axonal transport and proliferation or activation of opioid receptors may be enhanced by inflammatory mechanisms [24, 25]. This inflammatory requirement may limit the usefulness of peripheral opioids in acute pain. Furthermore, axonal opioid receptors may be functionally less efficient than those located at peripheral nerve terminals [4].

In summary, this study has demonstrated prolongation of sensory and motor block suggestive of a local anaesthetic effect. However, the degree of improvement in anaesthesia is unlikely to render this technique clinically useful. In particular, we did not demonstrate a significant improvement in the quality of postoperative analgesia. The absence of a significant clinical effect is in keeping with the theoretical limitations of peripheral axonal administration of opioids in acute pain.

Acknowledgements

W.P.G. was in receipt of a clinical research fellowship from the Ulster, North Down and Ards Hospitals Trust. We thank Janssen Research Foundation and the Department of Anaesthesia, Royal Victoria Infirmary, Newcastle upon Tyne, for their assistance in measurement of plasma alfentanil concentrations.

References

1. Yaksh TL, Noueihed R. The physiology and pharmacology of spinal opiates. *Annual Review of Pharmacology and Toxicology* 1985; **25**: 433–462.
2. Sibinga NES, Goldstein A. Opioid peptides and opioid receptors in cells of the immune system *Annual Review of Immunology* 1988; **6**: 219–249.
3. Fields HL, Emson PC, Leigh BK, Gilbert RFT, Iversen LL. Multiple opiate receptor sites on primary afferent fibres. *Nature (London)* 1980; **284**: 351–353.
4. Stein C. Peripheral mechanisms of opioid analgesia. *Anesthesia and Analgesia* 1993; **76**: 182–191.
5. Viel EJ, Eledjam, JJ, De La Coussaye JE, D'Athis F. Brachial plexus block with opioids for postoperative pain relief: comparison between buprenorphine and morphine. *Regional Anesthesia* 1989; **14**: 274–278.
6. Gobeaux D, Landais A. Utilisation de deux morphiniques dans les blocs du plexus brachial. *Cahiers d'Anesthésiologie* 1988; **36**: 437–440.
7. Bourke DL, Furman WR. Improved postoperative analgesia with morphine added to axillary block solution. *Journal of Clinical Anesthesia* 1993; **5**: 114–117.
8. Viñoles CM, Cuenca P, Monsegur JC, Valloba FC. Adición de fentanilo a la mepivacaína en el bloqueo axilar del plexo braquial. Efectos sobre la calidad anestésica y analgésica postoperatoris. *Revista Espanola de Anestesiologica y Reanimacion* 1991; **38**: 87–89.
9. Racz H, Gunning K, Della Santa D, Forster A. Evaluation of the effect of perineuronal morphine on the quality of postoperative analgesia after axillary plexus block: a randomized double-blind study. *Anesthesia and Analgesia* 1991; **72**: 769–772.
10. Bovill JG. Opioids. In: Dundee JW, Clarke RSJ, McCaughey W, eds. *Clinical Anaesthetic Pharmacology*. Edinburgh: Churchill Livingstone, 1991; 203–230.
11. Hill DA, Campbell WI. Two approaches to axillary brachial plexus block. Loss of resistance to saline or paraesthesia? *Anaesthesia* 1992; **47**: 207–209.
12. Bromage PR. Mechanism of action. In: Bromage PR, ed. *Epidural analgesia*. Philadelphia: WB Saunders, 1978; 119–159.
13. Bower S, Hull CJ. Comparative pharmacokinetics of fentanyl and alfentanil. *British Journal of Anaesthesia* 1982; **54**: 871–877.
14. Hassan AHS, Przewlocki R, Herz A, Stein C. Dynorphin, a preferential ligand for kappa-opioid receptors, is present in nerves fibers and immune cells within inflamed tissue of the rat. *Neuroscience Letters* 1992; **140**: 85–88.
15. Gobeaux D. Landais A, Bexon G, Cazaban J, Levron JC. Adjonction de fentanyl á la lidocaîne adrénalinée pour le blocage du plexus brachial. *Cahiers d'Anesthésiologie* 1987; **35**: 195–199.
16. Ben Ameur MB, Ecoffey C, Kuhlman G, Mazoit X, Gobeaux D. Réponse ventilatoire au dioxyde de carbone après axillaire avec fentanyl et fentanyl et lidocaîne. *Annales Francaises D'Anesthésiologie et de Réanimation* 1993; **12**: 22–26.
17. Ausems ME, Hug CC jr, Stanski DR, Burm AGL. Plasma concentrations of alfentanil required to supplement nitrous oxide anesthesia for general surgery. *Anesthesiology* 1986; **65**: 362–373.
18. Frank GB. Stereospecific opioid drug receptors on excitable cell membranes. *Canadian Journal of Physiology and Pharmacology* 1985; **63**: 1023–1032.
19. Power I, Brown DT, Wildsmith JAW. The effect of fentanyl, meperidine and diamorphine on nerve conduction in vitro. *Regional Anesthesia* 1991; **16**: 204–208.
20. Gissen AJ, Gugino LD, Datta S, Miller J, Covino BG. Effects of fentanyl and sufentanil on peripheral mammalian nerves. *Anesthesia and Analgesia* 1987: **66**: 1272–1276.
21. Yaksh TL. Substance P release from knee joint afferent terminals: modulation by opioids. *Brain Research* 1988; **458**: 319–324.
22. Czlonkowski A, Stein C, Herz A. Peripheral mechanisms of opioid antinociception in inflammation: involvement of cytokines. *European Journal of Pharmacology* 1993; **242**: 229–235.
23. Stein C, Hassan AHS, Przewlocki R, Gramasch C, Peter K, Herz A. Opioids from immunocytes interact with receptors on sensory nerves to inhibit nociception in inflammation. *Proceeds of the National Academy of Science USA* 1990; **87**: 5935–5939.
24. Young WS, Wamsley JK, Zarbin MA, Kuhar MJ. Opioid receptors undergo axonal flow. *Science* 1980; **210**: 76–77.
25. Laduron PM. Axonal transport of opiate receptors in capsaicin-sensitive neurones. *Brain Research* 1984; **294**: 157–160.

British Journal of Anaesthesia 1996; **76**: 806–810

Analgesic and anti-inflammatory effects of lignocaine–prilocaine (EMLA) cream in human burn injury

J. L. PEDERSEN, T. CALLESEN, S. MØINICHE AND H. KEHLET

Summary

Pain relief may be improved by reducing sensitization of nociceptive pathways caused by tissue injury. Such a reduction depends mainly on inhibition of local inflammatory changes and the relation between duration of nociceptive block and nociceptive input. In this study we examined if prolonged topical treatment with local anaesthetics could reduce late hyperalgesia and local inflammation after burn injury in healthy volunteers. The effects of EMLA treatment for 8 h after burn on hyperalgesia, inflammation and wound healing were compared with the contralateral placebo-treated leg for 48 h after bilateral burn injuries (15 × 25 mm, 49 °C for 5 min) in a double-blind, randomized study in 12 healthy volunteers. Wound healing was studied 1 and 2 weeks after injury. Neither mechanical nor thermal primary hyperalgesia were affected significantly by prolonged EMLA treatment. Secondary hyperalgesia and skin erythema were also not changed. Seven of 12 placebo-treated legs developed blisters, in contrast with four of 12 EMLA-treated legs. Wound healing showed no apparent differences. Our data suggest that prolonged, topical treatment with local anaesthetics did not reduce local inflammation and late hyperalgesia. (*Br. J. Anaesth.* 1996; **76**: 806–810)

Key words

Burns. Anaesthetics local, EMLA. Pain, mechanism.

Injury causes inflammation and may lead to prolonged sensitization of nociceptive pathways. Primary and secondary hyperalgesia are well established aspects of this process. Hyperalgesia describes the phenomenon of increased pain intensity in response to normally painful stimuli [1], primary hyperalgesia refers to the changes in sensation within the injury, while secondary hyperalgesia refers to sensory changes in the undamaged tissue surrounding the injury. Several inflammatory mediators promote hyperalgesia by sensitization of nociceptors [2].

Many *in vitro* and animal studies have shown anti-inflammatory effects of local anaesthetics and these effects may potentiate the analgesic effect of these agents. The anti-inflammatory effects may impair the host defence, but may also improve conditions with destructive inflammation. In contrast, there are only few human reports on the anti-inflammatory effects of local anaesthetics and we have shown previously that brief (3.5 h) topical treatment with local anaesthetics before and after injury did not significantly affect inflammation after burn [3]. The aim of the study was therefore to examine if prolonged and intense treatment with lignocaine–prilocaine cream (EMLA) could reduce late hyperalgesia and other markers of local inflammation after burn injury in healthy volunteers. The treatment was initiated after the burn, as this mimics the clinical situation.

Subjects and methods

We studied 12 healthy volunteers, aged 22–47 yr (all male), after obtaining informed consent and approval from the local Ethics Committee and the Danish National Health Board. Subjects were not medically knowledgeable and were not aware of the purpose of the study.

Baseline measurements, which included assessment of skin colour, mechanical pain detection threshold (MPDT) and heat pain detection threshold (HPDT), were performed on the medial calf in both legs. After obtaining baseline measurements, thermal injury was induced on each leg. All measurements, that is skin erythema, blister formation, MPDT, secondary hyperalgesia and HPDT, were made in this order, 16, 20, 24 and 48 h after the injuries. Immediately after the injury, EMLA or placebo was applied, double-blind and randomized, to the skin and covered under occlusive dressing for 8 h after the injury. Experiments were performed in a quiet room, temperature 20–22 °C, with subjects in a relaxed and reclined position. Subjects were instructed to keep their eyes closed during all measurements so that they had no impression of the results of the measurements.

EMLA TREATMENT

EMLA cream 2 g (2.5% prilocaine and 2.5% lignocaine eutectic mixture, Astra, Södertälje, Sweden) or placebo (Astra; Södertälje, Sweden) was applied in a double-blind, randomized manner to the skin and covered under occlusive dressing (Tegaderm, 3M Health Care Ltd, Leicestershire, UK) for 8 h after the injury. The cream was renewed

---

JURI L. PEDERSEN, MD, TORBEN CALLESEN, MD, HENRIK KEHLET, MD, PHD (Department of Surgical Gastroenterology); STEEN MØINICHE, MD (Department of Anaesthesiology); Hvidovre Hospital, University of Copenhagen, Kettegaard Allé 30, 2650 Hvidovre, Denmark. Accepted for publication: January 24, 1996.
Correspondence to J. L. P.

3 and 5.5 h after initial application, and re-covered. Subjects were instructed to avoid physical activities that could displace the thick cream layer from the injury. The burns were performed in the afternoon and the cream was removed 8 h later (late evening). Subjects attended next morning for the first measurement, 16 h after the injury.

THERMAL INJURY

Thermal injuries were produced on the medial surface of the right and left calf with a 15 × 25-mm Peltier thermode (Thermotest, Somedic A/B, Stockholm, Sweden). The thermode (49 °C) was applied to the skin for 5 min under standardized pressure (34 mm Hg), causing first- and superficial second-degree burn injuries [4, 5]. The burn caused immediate intense stinging pain, which was followed by a moderate burning pain with a more diffuse quality during the remainder of the stimulation period. Spontaneous pain after the injury has not been observed in the model.

PRIMARY HYPERALGESIA

Mechanical pain detection threshold (MPDT) within the injured area was determined by pinprick with nine progressively rigid von Frey hairs (Somedic A/B, Stockholm, Sweden). We examined the force produced by each hair by pressing it against a balance and measured the weight it produced when it was slightly flexed. We confirmed that the steps from 1 to 9 represented logarithmic increases in force (hair no. 1 = 3 mN, 2 = 9 mN, 3 = 11 mN, 4 = 18 mN, 5 = 29 mN, 6 = 49 mN, 7 = 98 mN, 8 = 98 mN, 9 = 175 mN). MPDT was defined as the lowest force (pinprick) which produced a definite sensation of pain or discomfort. Pinprick was performed with *each* hair from the thinnest, 8–10 times in the area of the injury, until *some* of the 8–10 stimulations were reported to be painful or unpleasant. The number of the hair producing pain was recorded and the procedure was repeated three times at each measurement point. The median of three threshold measurements was reported as the MPDT. If hair No. 9 did not produce any pain or discomfort, we assigned this observation the value 10.

Thermal thresholds were determined with the computerized Thermotest (Somedic A/B, Stockholm, Sweden) in the area of the injury. Heat pain detection threshold (HPDT) was the lowest temperature perceived as painful. Subjects were instructed to press a button as soon as the specified sensation was reached. Thermal thresholds were determined from a baseline of 32 °C with a rate of change of 1 $°C\,s^{-1}$. The upper cut-off limit was 52 °C. HPDT was calculated as the average of three measurements, with intervals of 9 s between each stimulation.

SECONDARY HYPERALGESIA

The area of mechanical hyperalgesia that developed around the burn injury was assessed with von Frey hair No. 9 (175 mN). In most cases pinprick with this hair is a painful or unpleasant stimulus in distinct spots of the skin, although it is not universally painful. Thus areas of hyperalgesia were measured, not areas of allodynia. Borders of hyperalgesia were determined by stimulating along eight radial linear paths arranged from the centre of injury. Stimulation along each path began well outside the hyperalgesic area where slight or no pain was perceived and continued slowly towards the centre of the burn injury until the subject reported a definite change in sensation, most often to a more intense pricking with a burning after-sensation. This point was marked and the eight marks were later traced onto a clear acetate sheet. The area of secondary hyperalgesia was calculated from the eight marks using a vector algorithm.

INFLAMMATION

In order to estimate the severity of inflammation, the intensity of erythema inside the injury was assessed with a hand-held skin reflectance spectrophotometer (Dermaspectrometer, Cortex Technology, Hadsund, Denmark) [6, 7]. The spectrophotometer provided a skin erythema index based on the absorption characteristics of green and red light in the skin. Measurements were performed in six spots within the burn injury. All values were recorded and the mean calculated. The development of blisters was recorded as present or absent. Healing of the burns was documented using a questionnaire, 1 and 2 weeks after the injury.

STATISTICAL ANALYSIS

Distribution of data was evaluated with the Shapiro Wilk test [8]. Primary mechanical hyperalgesia and secondary hyperalgesia in EMLA- and placebo-treated legs were evaluated at separate times with multiple Wilcoxon tests for paired observation with Bonferroni correction and area under the curves (AUC) for the whole observation period with Student's t test for differences in a paired design [9]. Evaluation of primary thermal hyperalgesia and erythema was based on AUC values but analysed also using parametric two-way analysis of variance (ANOVA) for repeated measurements [8]. Minimal differences between treatments detectable in the present study with a power of 90 % and a type I error of 5 % were evaluated with Student's t test for differences in a paired design [8]. $P < 0.05$ was considered statistically significant.

Results

The area of hyperalgesia surrounding the injury was not significantly altered by EMLA treatment compared with placebo (fig. 1A). The effect of EMLA was evaluated at all times (16 h, $P = 0.68$; 20 h, $P = 0.37$; 24 h, $P = 0.14$; and 48 h, $P = 0.07$; Wilcoxon test). The level of significance was reduced to 1 % in these comparisons with Bonferroni correction, because of the multiple comparisons. The area under the curve (AUC) for hyperalgesia was applied as a

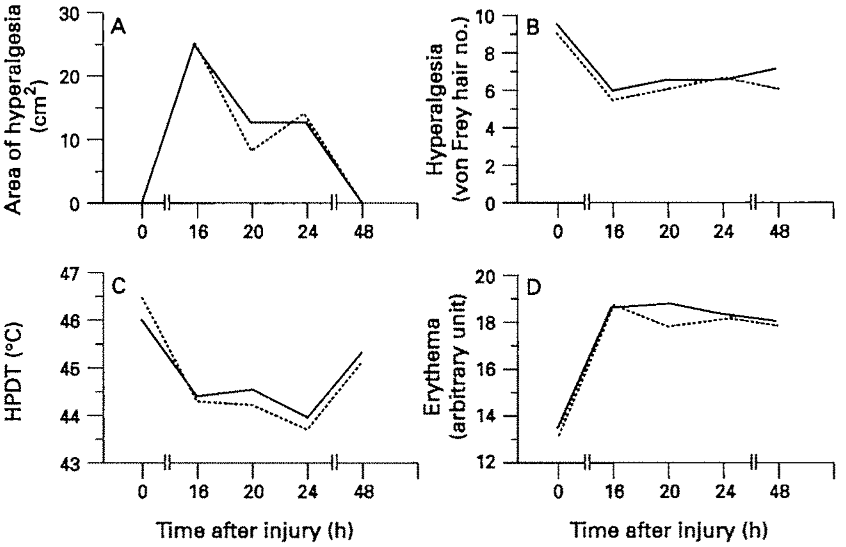


Figure 1 A: Secondary hyperalgesia, that is area of hyperalgesia to von Frey pinprick (175 mN) outside the injury, after burn injury in healthy volunteers treated with EMLA (· · · ·) or placebo (——). Time 0 h = measurements before thermal injury. Values are medians. Comparison of AUC values revealed no significant difference between secondary hyperalgesia in EMLA- *vs* placebo-treated legs ($P = 0.18$; Student's paired *t* test, $n = 12$). B: Primary mechanical hyperalgesia, that is mechanical pain detection threshold to von Frey pinprick, in the area of the burn injury. Values are medians. Comparison of AUC values revealed no significant difference between primary mechanical hyperalgesia in EMLA- (· · · ·) *vs* placebo- (——) treated legs ($P = 0.19$; Student's paired *t* test, $n = 12$). Von Frey hair no. (1–10) represents a rank scale, where 1 indicates a force of about 3 mN and 9 about 175 mN, whereas 10 indicates that 175 mN did not produce pain or discomfort. The steps from 1 to 9 are logarithmic increases in force (see text). C: Primary thermal hyperalgesia, that is heat pain detection threshold (HPDT) in the area of the burn injury. Values are means. Comparison revealed no significant difference between primary thermal hyperalgesia in EMLA (· · · ·)- *vs* placebo (——)-treated legs ($P = 0.61$; parametric two-way analysis of variance for repeated measurements, $n = 12$). D: Skin erythema, that is the intensity of erythema inside the burn injury assessed with a hand-held skin reflectance spectrophotometer. Values are means. Comparison revealed no significant difference between erythema in EMLA (· · · ·)- *vs* placebo (——)-treated legs ($P = 0.34$; parametric two-way analysis of variance for repeated measurements, $n = 12$).

Table 1 Positive answers out of 12, in a questionnaire (yes/no) completed by the 12 subjects

Changes in injury	Placebo (1 week)	EMLA (1 week)	Placebo (2 weeks)	EMLA (2 weeks)
Tenderness	1	0	0	0
Irritated by touch	2	0	0	0
Itch	3	2	3	1
Any colour change	7	9	6	5
Crusts	3	3	3	1
Blister	2	2	1	0
Skin erythema	6	6	4	0

Table 2 Minimum differences between treatments detectable with a power of 90% (type II error of 10%) and a type I error of 5%. Differences are presented as the weighted mean for the observation period (AUC divided by 48 h)

Secondary hyperalgesia (cm²)	Primary mechanical hyperalgesia (von Frey No.)	Primary thermal hyperalgesia (°C)	Erythema index (arb. unit)
13	0.9	2.4	1.3

summary measure of the total hyperalgesic response. AUC for secondary hyperalgesia after EMLA treatment was not significantly different from that after placebo ($P = 0.18$; Student's paired *t* test).

The effect of EMLA on primary mechanical hyperalgesia (fig. 1B) was analysed in the same way and there was no significant differences between EMLA and placebo (0 h, $P = 0.20$; 16 h, $P = 0.28$; 20 h, $P = 0.29$; 24 h, $P = 1.00$; and 48 h, $P = 0.25$; Wilcoxon test). Comparison of AUC values confirmed this finding ($P = 0.19$; Student's paired *t* test).

Data for primary thermal hyperalgesia (fig. 1C) and skin erythema index (fig. 1D) were analysed with both AUC summaries and parametric two-way ANOVA for repeated measurements. There were no significant differences between EMLA and placebo with both methods (primary thermal hyperalgesia: AUC, $P = 0.80$ and ANOVA, $P = 0.61$; and erythema: AUC, $P = 0.54$ and ANOVA, $P = 0.34$). Seven of 12 placebo-treated legs developed blisters in contrast with four of 12 EMLA-treated legs. With binomial data (yes/no), these small numbers precluded a sensible statistical analysis. There were no apparent differences in wound healing between EMLA and placebo treatment (table 1).

Minimal differences between treatments detectable in this study, with a power of 90 % and a type I error of 5 %, are presented in table 2. Differences are presented as the weighted mean for the observation period (AUC divided by 48 h).

Discussion

We examined if prolonged and intensive topical treatment with local anaesthetics reduced late hyperalgesia, blister formation or erythema after thermal injury in healthy volunteers in a double-blind, randomized study. We found that the local anaesthetics neither reduced local inflammation and late hyperalgesia nor produced apparent changes in wound healing, although the sample size does not exclude minor differences. This result may seem surprising, considering the known anti-inflammatory effects of local anaesthetics. Several *in vitro* studies have demonstrated reduced production of free oxygen radicals from polymorphonuclear leucocytes after treatment with local anaesthetics [10–14], and reduced adherence and migration of leucocytes have been documented in different *in vivo* models [15–18]. Furthermore, local anaesthetics inhibit movement of leucocytes and phagocytosis *in vitro* [14, 19–21]. Local anaesthetics have also been shown to reduce albumin extravasation in rats after burn injury and chemical peritonitis [22, 23] and to modify the inflammatory response to experimental colitis [24] and irradiation [25].

Local anaesthetics may alter release of inflammatory mediators, for example histamine release from mast cells *in vitro* [26], leukotriene B-4 and interleukin-1 release from polymorphonuclear granulocytes and mononuclear cells *in vitro*, respectively [27]. The flare reaction induced by trauma and injection of inflammatory mediators is diminished by local anaesthetics, in contrast with the weal and local red reaction [28–30]. Thus local anaesthetics block axon reflexes and sensory functions of nociceptors. Inhibition of axon reflexes reduces local, indirect release of inflammatory neuropeptides, but the clinical importance of diminished neurogenic inflammation is unclear. It is not known if the local effector function of directly stimulated nociceptors is affected by local anaesthetics [31]. Furthermore, local anaesthetics have been shown to inhibit substance P receptor binding [32]. Thus several anti-inflammatory effects of local anaesthetics have been demonstrated *in vitro* and in animal models, but evidence of effects in human studies is, to our knowledge, restricted to one uncontrolled study and one case report, where lignocaine improved ulcerative proctitis and severe interstitial cystitis, respectively [33, 34]. Topical lignocaine has been tested several times in asthmatic subjects with conflicting, but mainly negative results [35–37]. Topical lignocaine had no effects on allergen-induced nasal secretion, blood flow or obstruction, in allergic individuals [38]. We have shown earlier that short-lived topical application, or subcutaneous infiltration with local anaesthetics, did not affect inflammation after burn [3]. This study, with prolonged and intensive treatment, supports this conclusion. Our findings, and the lack of other clinical evidence, may therefore question the relevance of the anti-inflammatory effects of local anaesthetics.

There may be different explanations for our results. First, the response involves several inflammatory mediators and cell types, which may not be affected by local anaesthetics. Second, the timing of the treatment (before compared with after injury) may be important in modulating inflammatory responses, as early mediators release cascades of secondary mediators. In this study we preferred treatment after injury, as this mimics most clinical situations, while treatment was initiated before injury in our first study [3]. Apparently, this did not affect the results. Third, the effects of prolonged topical treatment were either too transient or incapable of altering the course of the inflammatory response. Although the analgesic effects did not last into the observation period (16–48 h after injury), we do not question the effectiveness of EMLA cream in pain relief, but effects on hyperalgesia should *not* be expected for prolonged periods (more than 8 h) after removal of the cream. The potential reduction of leukotriene B-4, interleukin-1, histamine, free oxygen radicals and activated leucocytes by local anaesthetics [27] should attenuate sensitization of nociceptors in the injury, but removal of EMLA cream 8 h before the first measurements may have returned the process to its natural course. Fourth, we studied only 12 subjects and we may have missed some real differences. The minimal differences between treatments detectable in this study, with a power of 90 %, are shown in table 2.

The consequences for wound healing after treatment with local anaesthetics are controversial. The synthesis of collagen and glycosaminoglycans by fibroblasts *in vitro* is reduced by local anaesthetics [39], as is the tensile strength of skin wounds in rats [40]. Other studies [41], including our own, have been unable to demonstrate adverse clinical effects on host defences and wound healing, but our study is less specific in this respect than the first mentioned studies, and prolonged use of local anaesthetics may threaten tissue defences.

Acknowledgements

The study was supported by grants from the John and Birte Meyer Foundation, the P. A. Messerschmidt and Wife's Fund, Fonden til Laegevidenskabens Fremme and Astra Pain Control, Södertälje, Sweden.

References

1. Lindblom U, Merskey H, Mumford JM, Nathan PW, Noordenbos W, Sunderland SS. Pain terms. A current list with definitions and notes on usage. *Pain* 1986; (Suppl. 3): S215–S221.
2. Dray A. Inflammatory mediators of pain. *British Journal of Anaesthesia* 1995; **75**: 125–131.
3. Møiniche S, Dahl JB, Brennum J, Kehlet H. No anti-inflammatory effect of short-term topical and subcutaneous administration of local anesthetics on postburn inflammation. *Regional Anesthesia* 1993; **18**: 300–303.
4. Møiniche S, Dahl JB, Kehlet H. Time course of primary and secondary hyperalgesia after heat injury to the skin. *British Journal of Anaesthesia* 1993; **71**: 201–205.
5. Moritz AR, Henriques FC. Studies of thermal injury. II. The relative importance of time and surface temperature in the causation of cutaneous burns. *American Journal of Pathology* 1947; **23**: 695–720.
6. Bjerring P, Andersen PH. Skin reflectance spectrophotometry. *Photodermatology* 1987; **4**: 167–171.
7. Andersen PH, Bjerring P. Spectral reflectance of human skin in vivo. *Photodermatology, Photoimmunology and Photomedicine* 1990; **7**: 5–12.
8. Altman DG. *Practical Statistics for Medical Research*, 1st Edn. London: Chapman & Hall, 1991.
9. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *British Medical Journal* 1990; **300**: 230–235.
10. Cederholm I, Briheim G, Rutberg H, Dahlgren C. Effects of five amino-amide local anaesthetic agents on human polymorphonuclear leucocytes measured by chemiluminescence. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 704–710.

11. Ohsaka A, Saionji K, Sato N, Igari J. Local anesthetic lidocaine inhibits the effect of granulocyte colony-stimulating factor on human neutrophil functions. *Experimental Hematology* 1994; **22**: 460–466.
12. Goldstein IM, Lind S, Hoffstein S, Weissmann G. Influence of local anesthetics upon human polymorphonuclear leukocyte function in vitro. Reduction of lysosomal enzyme release and superoxide anion production. *Journal of Experimental Medicine* 1977; **146**: 483–494.
13. Kanbara T, Tomoda MK, Sato EF, Ueda W, Manabe M. Lidocaine inhibits priming and protein tyrosine phosphorylation of human peripheral neutrophils. *Biochemical Pharmacology* 1993; **45**: 1593–1598.
14. Vandenbroucke Grauls CM, Thijssen RM, Marcelis JH, Sharma SD, Verhoef J. Effects of lysosomotropic amines on human polymorphonuclear leucocyte function. *Immunology* 1984; **51**: 319–326.
15. Eriksson AS, Sinclair R, Cassuto J, Thomsen P. Influence of lidocaine on leukocyte function in the surgical wound. *Anesthesiology* 1992; **77**: 74–78.
16. Giddon DB, Lindhe J. In vivo quantitation of local anesthetic suppression of leukocyte adherence. *American Journal of Pathology* 1972; **68**: 327–338.
17. Paul H, Clayburne G, Schumacher HR. Lidocaine inhibits leukocyte migration and phagocytosis in monosodium urate crystal-induced synovitis in dogs. *Journal of Rheumatology* 1983; **10**: 434–439.
18. MacGregor RR, Thorner RE, Wright DM. Lidocaine inhibits granulocyte adherence and prevents granulocyte delivery to inflammatory sites. *Blood* 1980; **56**: 203–209.
19. Moudgil GC, Allan RB, Russell RJ, Wilkinson PC. Inhibition, by anaesthetic agents, of human leucocyte locomotion towards chemical attractants. *British Journal of Anaesthesia* 1977; **49**: 97–105.
20. Hammer R, Dahlgren C, Stendahl O. Inhibition of human leucocyte metabolism and random mobility by local anaesthesia. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 520–523.
21. Cullen BF, Haschke RH. Local anesthetic inhibition of phagocytosis and metabolism of human leukocytes. *Anesthesiology* 1974; **40**: 142–146.
22. Cassuto J, Nellgård P, Stage L, Jönsson A. Amide local anesthetics reduce albumin extravasation in burn injuries. *Anesthesiology* 1990; **72**: 302–307.
23. Rimbäck G, Cassuto J, Wallin G, Westlander G. Inhibition of peritonitis by amide local anesthetics. *Anesthesiology* 1988; **69**: 881–886.
24. McCafferty DM, Sharkey KA, Wallace JL. Beneficial effects of local or systemic lidocaine in experimental colitis. *American Journal of Physiology* 1994; **266**: G560–567.
25. Ohlsén L, Evers H, Segerström K, Hagelqvist E, Graffman S. Local anaesthetics modifying the dermal response of irradiation. An experimental study. *Acta Oncologica* 1987; **26**: 467–476.
26. Johnson HG, Miller MD. Inhibition of histamine release and ionophore-induced calcium flux in rat mast cells by lidocaine and chlorpromazine. *Agents and Actions* 1979; **9**: 239–243.
27. Sinclair R, Eriksson AS, Gretzer C, Cassuto J, Thomsen P. Inhibitory effects of amide local anaesthetics on stimulus-induced human leucocyte metabolic activation, LTB4 release and IL-1 secretion in vitro. *Acta Anaesthesiologica Scandinavica* 1993; **37**: 159–165.
28. Wallengren J, Håkanson R. Effects of capsaicin, bradykinin and prostaglandin E2 in the human skin. *British Journal of Dermatology* 1992; **126**: 111–117.
29. Harper EI, Beck JS, Spence VA. Effect of topically applied local anaesthesia on histamine flare in man measured by laser Doppler velocimetry. *Agents and Actions* 1989; **28**: 192–197.
30. Pipkorn U, Andersson M. Topical dermal anaesthesia inhibits the flare but not the weal response to allergen and histamine in the skin-prick test. *Clinical Allergy* 1987; **17**: 307–311.
31. Maggi CA. Tachykinins and calcitonin gene-related peptide (CGRP) as co-transmitters released from peripheral endings of sensory nerves. *Progress in Neurobiology* 1995; **45**: 1–98.
32. Li YM, Wingrove DE, Too HP, Marnerakis M, Stimson ER, Strichartz GR, Maggio JE. Local anesthetics inhibit substance P binding and evoked increases in intracellular Ca^{2+}. *Anesthesiology* 1995; **82**: 166–173.
33. Björck S, Dahlström A, Johansson L, Ahlman H. Treatment of the mucosa with local anaesthetics in ulcerative colitis. *Agents and Actions* 1992; (Spec No): C60–C72.
34. Asklin B, Cassuto J. Intravesical lidocaine in severe interstitial cystitis. Case report. *Scandinavian Journal of Urology and Nephrology* 1989; **23**: 311–312.
35. Caire N, Cartier A, Ghezzo H, L'Archeveque J, Malo JL. Inhaled lignocaine does not alter bronchial hyperresponsiveness to hyperventilation of dry cold air in asthmatic subjects. *Clinical and Experimental Allergy* 1989; **19**: 65–70.
36. McAlpine LG, Thomson NC. Lidocaine-induced bronchoconstriction in asthmatic patients. Relation to histamine airway responsiveness and effect of preservative. *Chest* 1989; **96**: 1012–1015.
37. Prakash GS, Sharma SK, Pande JN. Effect of 4% lidocaine inhalation in bronchial asthma. *Journal of Asthma* 1990; **27**: 81–85.
38. Holmberg K, Bake B, Pipkorn U. The effect of topical nasal anaesthesia on allergen-induced symptoms, obstruction and blood flow. *Clinical and Experimental Allergy* 1989; **19**: 443–447.
39. Chvapil M, Hameroff SR, O'Dea K, Peacock EE jr. Local anesthetics and wound healing. *Journal of Surgical Research* 1979; **27**: 367–371.
40. Morris T, Tracey J. Lignocaine: its effects on wound healing. *British Journal of Surgery* 1977; **64**: 902–903.
41. Brofeldt BT, Cornwell P, Doherty D, Batra K, Gunther RA. Topical lidocaine in the treatment of partial-thickness burns. *Journal of Burn Care and Rehabilitation* 1989; **10**: 63–68.

British Journal of Anaesthesia 1996; **76**: 811–815

Continuous extrapleural paravertebral infusion of bupivacaine for post-thoracotomy analgesia in young infants

M. K. KARMAKAR, P. D. BOOKER, R. FRANKS AND M. POZZI

Summary

We have studied the efficacy of a continuous paravertebral infusion of bupivacaine for the management of post-thoracotomy pain in 20 infants with a median age of 5.3 weeks (range 2 days to 20 weeks). Immediately before chest closure, 0.25% bupivacaine 1.25 mg kg^{-1} was injected into an extrapleural paravertebral catheter, inserted under direct vision. A continuous infusion of 0.25% bupivacaine 0.5 mg kg^{-1} h^{-1} was commenced 1 h later and terminated after 24 h. We found that extrapleural paravertebral catheter placement under direct vision was easy in neonates and infants. The technique provided effective postoperative pain relief in 18 (90%) patients and the failure in two (10%) infants was attributed to catheter block. Mean maximum serum concentrations of bupivacaine after the loading dose and during infusion were 1.03 (SD 0.56) and 2.00 (0.63) µg ml^{-1}, respectively. There were no major complications relating to the technique and we conclude that extrapleural paravertebral block is a simple and effective method for post-thoracotomy analgesia in young infants. (*Br. J. Anaesth.* 1996; **76**: 811–815).

Key words

Anaesthetic technique, regional, paravertebral. Anaesthetics local, bupivacaine. Anaesthesia, paediatric. Pain, postoperative. Surgery, thoracic. Infants.

Providing safe and effective analgesia after thoracotomy in infants is particularly difficult. Opioids are the mainstay of treatment of such pain [1, 2], although the potential for serious respiratory depression [3] may lead to inadequate prescribing or administration, or both, in young children [4–6]. Despite the increasing interest in regional anaesthesia to provide postoperative pain relief in children, the use of percutaneous paravertebral analgesia has only been reported recently in this age group [7, 8]. Insertion of the paravertebral catheter under direct vision at the time of thoracotomy [9, 10] appears to provide equally effective analgesia to the percutaneous approach but is an easier and safer technique. Prompted by these encouraging preliminary reports, we undertook a prospective, non-comparative study to assess the safety and efficacy of a continuous extrapleural paravertebral infusion of bupivacaine in young infants after thoracotomy. As a continuous infusion of bupivacaine into a vascular site, such as the paravertebral space, has the potential to lead to significant systemic absorption and accumulation, we measured serum concentrations of bupivacaine intermittently throughout the study.

Patients and methods

The study was approved by the local Ethics Committee and written informed parental consent was obtained before operation. We studied 20 infants less than 4 months of age (neonates included) who were > 38 weeks' gestational age undergoing elective or emergency thoracotomy for various cardiac procedures. Patients were excluded if they were < 2.5 kg in weight, their immediate postoperative care was anticipated to be other than in the intensive care unit (ICU) or if they were expected to require postoperative artificial ventilation.

No premedication was prescribed. I.v. cannulation was performed before anaesthesia which was induced with thiopentone 4–5 mg kg^{-1}. Atracurium 0.5 mg kg^{-1} was used to facilitate tracheal intubation. Anaesthesia was maintained with 0.5% isoflurane and 50–66% nitrous oxide in oxygen, and i.v. fentanyl 2 µg kg^{-1} was used to provide preoperative analgesia. Cannulation of the right radial artery was performed to facilitate arterial pressure monitoring and sampling for bupivacaine assays.

Immediately before chest closure, the parietal pleura was peeled medially starting at the thoracotomy space. The resulting pocket was extended from the posterior wound margin onto the vertebral bodies and for two intercostal spaces above and two below. A Lahey's forceps was used to create a tunnel in the paravertebral space. An appropriately sized Tuohy needle was inserted percutaneously at a site close to the angle of the rib of the thoracotomy incision to emerge near the extrapleural pocket created earlier. The needle was removed and either an end-holed (od 0.63 mm) or side holed (od 0.9 mm) extradural catheter (minipack, Portex Ltd) was advanced through the needle and positioned cranially under direct vision such that about 3 cm of its length lay against the costo-vertebral joints within the

---

M. K. KARMAKAR*, FRCA, P. D. BOOKER, FRCA, R. FRANKS, FRCS, M. POZZI, MD, Royal Liverpool Children's NHS Trust, Eaton Road, Liverpool L12 2AP. Accepted for publication: February 13, 1996.

*Present address: Tawam Hospital, PO Box 15258, Al Ain, Abu Dhabi, United Arab Emirates.

Correspondence to P.D.B.

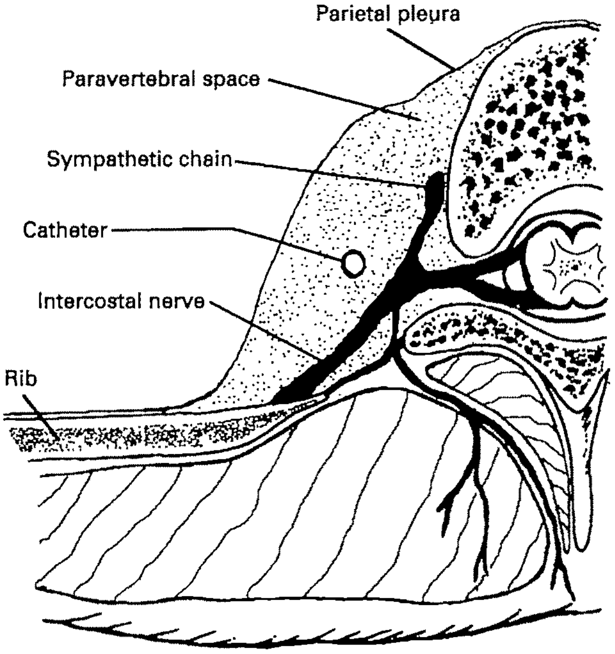


Figure 1 Position of the catheter in relation to the anatomy of the paravertebral space.

pocket (see fig. 1). The needle was removed and the parietal pleura was re-attached to the posterior edge of the wound before the thorax was closed. The catheter was affixed securely to the skin where it emerged through the chest wall and a bacterial filter attached.

The catheter was aspirated to examine for the absence of cerebrospinal fluid or blood. A test dose of 0.125% bupivacaine with adrenaline 1:400000 (1.0 ml) was injected and haemodynamic variables recorded for 5 min. When intravascular catheter placement had been excluded, a loading dose of 0.25% bupivacaine 0.5 ml kg^{-1} (1.25 mg kg^{-1}) was injected into the catheter. Haemodynamic variables were recorded 1, 3, 5, 10, 15 and 30 min after the loading dose. The infant was transferred to the ICU and the trachea extubated when clinically appropriate, usually within 1–2 h. One hour after administration of the loading dose a continuous infusion of 0.25% bupivacaine 0.2 ml kg^{-1} h^{-1} (0.5 mg kg^{-1} h^{-1}) was commenced and continued for 24 h, except in two patients where the infusion was continued for 36 h. Thereafter, paracetamol was prescribed in accordance with routine clinical practice. Hourly assessments of postoperative pain were made by a nurse not otherwise involved in the care of the patient, using a modified CRIES pain score [11]. An i.v. infusion of morphine 10 μg kg^{-1} h^{-1} was prescribed as "rescue analgesia", only if a pain score > 3 was recorded (maximum score = 10) and could not be reduced by a dummy or verbal soothing.

Arterial blood samples (1 ml) were obtained at 10-min intervals for 60 min after the loading dose and at 6-h intervals for 24 h after starting the infusion, for measurement of serum concentrations of bupivacaine. Blood samples were centrifuged, the serum separated and stored at −20 °C until assay. Serum concentrations of bupivacaine were measured by reverse phase high performance liquid chromatography using an Ultrasphere ods 5u, 150 × 4.6 mm column and 205 nm detector. The assay was calibrated with bupivacaine standard in methanol. Etidocaine or mepivacaine was used as the internal standard depending on the position of interfering peaks in the serum blank. A single extraction with methyl tert-butyl ether was performed. The limit of detection was 0.05 μg ml^{-1}. The coefficient of variation was ±4% at 0.05 μg ml^{-1} with a between-batch variability of 4%.

Results

The age, weight and operation performed on each patient are shown in table 1. Median age was 5.3 weeks (range 2 days to 20 weeks) and median weight 3.8 (range 2.5–6.2) kg. There were no difficulties related to insertion of the extrapleural paravertebral catheter under direct vision, even in the smallest neonate. The extrapleural fascia, which has been described in adults [12], was difficult to delineate in this age group, and therefore the catheters were inserted extrapleurally in the paravertebral space. There was no inadvertent intravascular catheter insertion in any patient, although blood-stained serous fluid, presumably from a collection in the extrapleural pocket, was aspirated before the test dose in almost every case. There were no adverse haemodynamic changes either after institution of the block or during infusion in any patient.

In 18 (90%) patients the mean hourly pain score was 0.52 (SD 0.33) and the median of the mean hourly pain score was 0.46 (range 0.0–1.4) (fig. 2); none of these patients required morphine as rescue analgesia after operation. Two patients (10%) had pain scores > 3 and therefore they both received morphine. In both of these patients the catheters were found to be either blocked or kinked, thereby preventing infusion of bupivacaine.

The maximum serum bupivacaine concentration ($C_S$max) measured during the first 60 min after the

Table 1 Patient data. PDA = Ligation/division of ductus arteriosus, MBTS = modified Blalock-Taussig shunt, COARC = repair of coarctation

Patient No.	Age (weeks)	Weight (kg)	Operation
1	14	4.7	PDA
2	14	4.9	MBTS
3	9.0	4.3	MBTS
4	16	5.0	COARC
5	2.3	3.8	COARC
6	1.1	2.6	MBTS
7	0.8	3.9	COARC
8	9.0	3.9	MBTS
9	7.9	3.5	COARC
10	0.3	3.1	MBTS
11	6.1	3.0	COARC
12	1.1	2.8	COARC
13	2.3	2.8	MBTS
14	1.2	3.3	MBTS
15	1.3	4.3	COARC
16	4.5	2.5	PDA
17	18	6.2	PDA
18	20	5.7	COARC
19	0.3	3.8	COARC
20	16	3.3	PDA
Median	5.3	3.8	

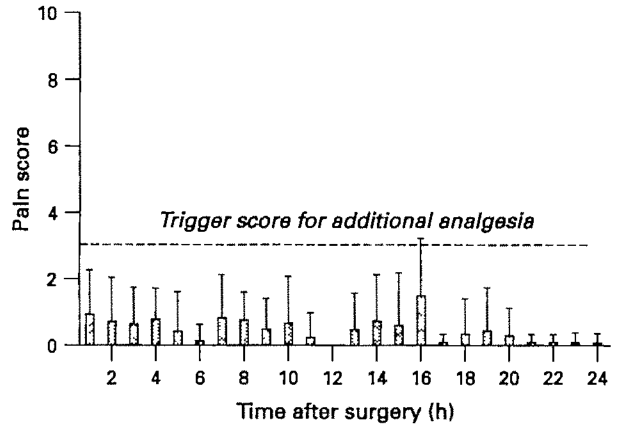


Figure 2 Mean (SD) hourly pain scores. Maximum score = 10.

Table 2 Maximum serum bupivacaine concentration and time to peak concentration for each patient after initial paravertebral injection of 0.25% bupivacaine 1.25 mg kg^{-1}. *SNO = Sample not obtained

Patient No.	Peak bupivacaine concn (μg ml^{-1})	Time to peak concn (min)
1	1.68	30
2	0.71	10
3	1.19	10
4	1.02	10
5	0.49	10
6	0.74	30
7	2.43	40
8	1.33	10
9	1.41	10
10	SNO	—
11	0.91	50
12	0.69	10
13	0.47	10
14	0.72	10
15	0.66	10
16	0.72	30
17	0.66	10
18	SNO	—
19	0.79	10
20	0.67	40
Mean (SD) or median (range)	1.03 (0.56)	10 (10–60)

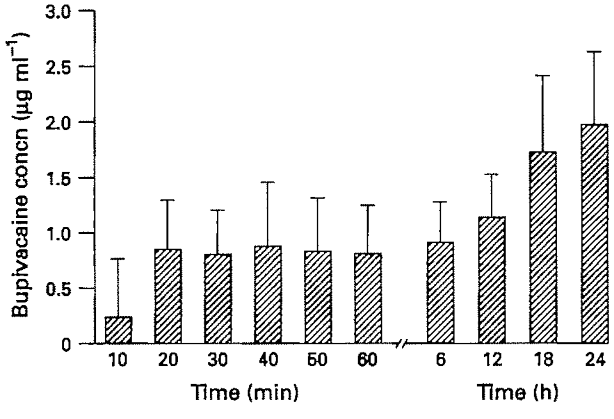


Figure 3 Mean (SD) serum bupivacaine concentrations during infusion.

Table 3 Mean (SD) [range] serum bupivacaine concentrations during continuous infusion of 0.25% bupivacaine 0.5 mg kg^{-1} h^{-1}

Time (h) from starting infusion	Bupivacaine concn (μg ml^{-1})	
6	0.92 (0.39)	[0.35–1.79]
12	1.16 (0.39)	[0.62–1.84]
18	1.75 (0.69)	[0.75–2.98]
24	2.00 (0.64)	[0.80–3.14]

initial injection and time to achieve this peak concentration (tC_Smax) are shown for 18 patients in table 2. Technical problems in two patients prevented sampling. Mean $C_S$max was 1.03 (0.56) μg ml^{-1} and median tC_Smax was 10 (range 10–60) min. A wide variation between individual patients was noted. After the initial peak after the first injection, there was a progressive increase in mean serum bupivacaine concentrations (fig. 3). Mean serum bupivacaine concentrations measured at 6, 12, 18 and 24 h (table 3) demonstrated wide variation between individual patients. Mean maximum serum bupivacaine measured at any time between 6 and 24 h after starting the infusion was 2.00 (SD 0.63) μg ml^{-1}.

There were no major complications relating either to the technique or the infusion. One patient had a transient ipsilateral Horner's syndrome which resolved after the infusion was stopped. Although there was evidence of accumulation of bupivacaine during the continuous infusion in many patients, none exhibited clinical signs suggestive of bupivacaine toxicity.

Discussion

We have confirmed that insertion of a paravertebral catheter, under direct vision at thoracotomy, is a safe technique, even in small neonates. A continuous infusion of bupivacaine into the catheter appears to provide effective postoperative analgesia for this procedure and this technique is now used routinely in our unit. However, we have shown that after 24 h there is evidence of significant accumulation of bupivacaine in some patients which, if the infusion had been continued for longer, may have reached potentially toxic concentrations [13–18]. The dose of bupivacaine used was the maximum safe infusion rate recommended for extradural block in children [15, 19]; preliminary results from an on-going study suggest that the concentration can be reduced without affecting efficacy.

Other regional techniques used to provide prolonged post-thoracotomy analgesia in children include continuous intercostal nerve block [20], thoracic extradural [21–23] and intrapleural catheter insertion [24, 25]. All of these methods have the disadvantages of either technical difficulty or unreliable efficacy. Advancement of a lumbar or caudal extradural catheter into the thoracic region, to avoid the possibility of spinal cord injury in the anaesthetized child having a direct thoracic extradural, has achieved some success [26, 27], although it may prove unreliable in infants [28]. Similarly, the use of continuous intercostal nerve block using catheters inserted during operation under direct vision [20] may fail to provide complete analgesia [29].

Paravertebral block should be more effective than more distal intercostal nerve block, as only the former reliably blocks the posterior primary rami and the ipsilateral sympathetic fibres [30], both of which are involved in the afferent inputs after thoracotomy. Paravertebral block, although originally described by Kappis in 1919 [31], received little attention until a continuous infusion technique was reported in 1979 [30]. This latter technique has since been used extensively in adults to provide safe, reliable and effective post-thoracotomy analgesia [10, 32–34]. The intercostal nerves, their collateral branches, especially the posterior primary rami and the thoracic sympathetic chain, pass through the paravertebral space making it an ideal site for afferent nociceptive block. Segmentation of the nerve into small bundles lying freely among the fat of the paravertebral space makes the nerves exceptionally favourable for block [35] and, furthermore, each space communicates superiorly and inferiorly, across the neck of the ribs, with the spaces above and below. This has been demonstrated in cadaver studies with resin [36], radiologically with contrast medium [37, 38] and clinically with the use of methylene blue at thoracotomy [10]. Although unilateral paravertebral spread of contrast medium without overspill into the pleural cavity or extradural space has been demonstrated [38], medial spread into the extradural space has also been shown [37, 39]. The role of this extradural spread remains unclear, but it may play a part in the extension of sensory block.

Paravertebral block has only recently been reported to provide effective post-thoracotomy analgesia in children, performed either percutaneously [8] or by inserting a catheter in the extrapleural paravertebral space under direct vision [9]. The technique has been shown to produce analgesia equal to or superior to extradural analgesia in children [7]. Although paravertebral block has been dismissed in many standard texts as being a hazardous technique [40, 41], these comments have been unsubstantiated by any evidence. In fact the complication rate for percutaneous paravertebral block in children (pleural puncture (2.08 %), vascular puncture (4.2 %) and an overall failure of rate of 6.2 % (3/48) [42]), can be compared favourably with other regional techniques used in this age group [43, 44]. Moreover, these complication and failure rates can be reduced further by performing catheter insertion under direct vision which we have found to be an effective technique in even the smallest neonate. We did not encounter any problem relating directly to the technique of catheter insertion; a similar lack of complications was reported in a study of six older children using this same method of analgesia [9].

In our study we found that the technique of continuous extrapleural paravertebral infusion of bupivacaine provided effective analgesia in 90 % (18/20) of our patients compared with the 100 % (6/6) success rate in older children reported by Eng and Sabanathan [9]. The 10 % (2/20) failure rate in our study was related to catheter blockage. The catheters used in both of these patients were designed to pass through a 19-gauge Tuohy needle, had only end holes and a tendency to kinking and blockage. The use of these particular catheters was therefore discontinued and slightly larger catheters (od 0.9 mm) with three lateral eyes, able to pass through an 18-gauge Tuohy needle, were used in all subsequent patients, however small, with a resultant 100 % success rate.

Acknowledgements

Financial support for the study was given by the Royal Liverpool Children's NHS Trust Research Fund.

References

1. Berde CB. Pediatric postoperative pain management. *Pediatric Clinics of North America* 1989; **36**: 921–940.
2. Lloyd-Thomas AR. Pain management in paediatric patients. *British Journal of Anaesthesia* 1990; **64**: 85–104.
3. Purcell-Jones G, Dormon F, Sumner E. The use of opioids in neonates. A retrospective study of 933 cases. *Anaesthesia* 1987; **42**: 1316–1320.
4. Beyer JE, DeGood DE, Ashley LC, Russel GA. Patterns of postoperative analgesic use with adults and children following cardiac surgery. *Pain* 1983; **17**: 71–81.
5. Mather LE, Mackie J. The incidence of postoperative pain in children. *Pain* 1983; **15**: 271–282.
6. Schechter NL, Allen DA, Hanson K. Status of paediatric pain control: a comparison of hospital analgesic usage in children and adults. *Paediatrics* 1986; **77**: 11–15.
7. Lonnqvist PA, Olsson GL. Paravertebral vs epidural block in children. Effects on postoperative morphine requirement after renal surgery. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 346–349.
8. Lonnqvist PA. Continuous paravertebral block in children. Initial experience. *Anaesthesia* 1992; **47**: 607–609.
9. Eng J, Sabanathan S. Continuous paravertebral block for postthoracotomy analgesia in children. *Journal of Pediatric Surgery* 1992; **27**: 556–557.
10. Sabanathan S, Bickford Smith PJ, Pradhan GN, Hashimi H, Eng J, Mearns AJ. Continuous intercostal nerve block for pain relief after thoracotomy. *Annals of Thoracic Surgery* 1988; **46**: 425–426.
11. Krechel SW, Bildner J. CRIES: a new neonatal postoperative pain measurement score. Initial testing of validity and reliability. *Paediatric Anaesthesia* 1995; **5**: 53–61.
12. Berrisford RG, Sabanathan S. Direct access to the paravertebral space at thoracotomy. *Annals of Thoracic Surgery* 1990; **49**: 854.
13. Eyres RL. Local anaesthetic agents in infancy. *Paediatric Anaesthesia* 1995; **5**: 213–218.
14. Berde CB. Convulsions associated with pediatric regional anesthesia. *Anesthesia and Analgesia* 1992; **75**: 164–166.
15. Berde CB. Bupivacaine toxicity secondary to continuous caudal epidural infusion in children. *Anesthesia and Analgesia* 1993; **77**: 1305–1306.
16. Agarwal R, Gutlove DP, Lockhart CH. Seizures occurring in pediatric patients receiving continuous infusion of bupivacaine. *Anesthesia and Analgesia* 1992; **75**: 284–286.
17. Larsson BA, Olsson GL, Lonnqvist PA. Plasma concentrations of bupivacaine in young infants after continuous epidural infusion. *Paediatric Anaesthesia* 1994; **4**: 159–162.
18. McCloskey JJ, Haun SE, Deshpande JK. Bupivacaine toxicity secondary to continuous caudal epidural infusion in children. *Anesthesia and Analgesia* 1992; **75**: 287–290.
19. Coombs RC, Morgan MEI, Durbin GM, Booth IW, McNeish AS. Gut blood flow velocities in the newborn: effects of patent ductus arteriosus and parenteral indomethacin. *Archives of Disease in Childhood* 1990; **65**: 1067–1071.
20. Cooper MG, Seaton HL. Intraoperative placement of intercostal catheter for post-thoracotomy pain relief in a child. *Paediatric Anaesthesia* 1992; **2**: 165–167.
21. Arthur DS. Postoperative thoracic epidural analgesia in children. *Anaesthesia* 1980; **35**: 1131.
22. Murat I, Delleur MM, Esteve C, Egu C, Raynaud P, Saint-Maurice C. Continuous extradural anaesthesia in children. *British Journal of Anaesthesia* 1987; **69**: 1441–1450.

23. Attia J, Ecoffey C, Sandouk P, Gross JB, Samii K. Epidural morphine in children: pharmacokinetics and CO_2 sensitivity. *Anesthesiology* 1986; **65**: 590–594.
24. McIlvaine WB, Knox RF, Fennessey PV, Goldstein M. Continuous infusion of bupivacaine via intrapleural catheter for analgesia after thoracotomy in children. *Anesthesiology* 1988; **69**: 261–264.
25. Weston PJ, Bourchier D. The pharmacokinetics of bupivacaine following interpleural nerve block in infants of very low birthweight. *Paediatric Anaesthesia* 1995; **5**: 219–222.
26. Bosenberg AT, Bland BAR, Schulte-Steinberg O, Downing JW. Thoracic epidural anesthesia via caudal route in infants. *Anesthesiology* 1988; **69**: 265–269.
27. Rasch DK, Webster DE, Pollard TG, Gurkowski MA. Lumbar and thoracic epidural analgesia via the caudal approach for postoperative pain relief in infants and children. *Canadian Journal of Anaesthesia* 1990; **37**: 359–362.
28. van Niekerk J, Bax-Vermiere BMJ, Geurts JVM, Kramer PPG. Epidurography in premature infants. *Anaesthesia* 1990; **45**: 722–725.
29. Safran D, Kuhlman G, Orhant EE, Castelain MH, Journois D. Continuous intercostal blockade with lidocaine after thoracic surgery. Clinical and pharmacokinetic study. *Anesthesia and Analgesia* 1990; **70**: 541–544.
30. Eason MJ, Wyatt R. Paravertebral thoracic block—a reappraisal. *Anaesthesia* 1979; **34**: 638–642.
31. Kappis M. Sensilität und lokale Anästhesie gebiet der Bauchole mit besonderer berücksichtigung der splanchnicus Anästhesie. *Beiträge zur Linichen Chirurgie* 1919; **115**: 161–175.
32. Mathews PJ, Govenden V. Comparison of continuous paravertebral and extradural infusion of bupivacaine for pain relief after thoracotomy. *British Journal of Anaesthesia* 1989; **62**: 204–205.
33. Sabanathan S, Mearns AJ, Bickford Smith PJ, Eng J, Berrisford RG, Bibby SR, Majid MR. Efficacy of continuous extrapleural intercostal nerve block on post-thoracotomy pain and pulmonary mechanics. *British Journal of Surgery* 1990; **77**: 221–225.
34. Richardson J, Sabanathan S, Eng J, Mearns AJ, Rogers C, Evans CS, Bembridge J, Majid MR. Continuous intercostal nerve block versus epidural morphine for post-thoracotomy analgesia. *Annals of Thoracic Surgery* 1993; **55**: 377–380.
35. Nunn JF, Slavin G. Posterior intercostal nerve block for pain relief after thoracotomy. Anatomical basis and efficacy. *British Journal of Anaesthesia* 1980; **52**: 253–260.
36. Conacher ID. Resin injection of thoracic paravertebral spaces. *British Journal of Anaesthesia* 1988; **61**: 657–661.
37. Conacher ID, Kokri M. Postoperative paravertebral block for thoracic surgery: a radiological appraisal. *British Journal of Surgery* 1987; **59**: 155–161.
38. Eng J, Sabanathan S. Site of action of continuous extrapleural intercostal nerve block. *Annals of Thoracic Surgery* 1991; **51**: 387–389.
39. Purcell-Jones G, Pither CE, Justins DM. Paravertebral somatic nerve block: a clinical, radiographic and computed tomographic study in chronic pain patients. *Anesthesia and Analgesia* 1989; **68**: 32–39.
40. Owens FB. Blocks of nerves of the trunk. In: Dalens BJ, ed. *Pediatric Regional Anesthesia*. Boca Raton: CRC Press, 1990; 441–464.
41. Littlewood DG. Regional anaesthesia of the trunk. In: Wildsmith JAW, Armitage EN, eds. *Principles and Practice of Regional Anaesthesia*. Edinburgh: Churchill Livingstone, 1987; 132.
42. Lonnqvist PA, MacKenzie J, Soni AK, Conacher ID. Paravertebral blockade. Failure rate and complications. *Anaesthesia* 1995; **50**: 813–815.
43. Broadman LM. Regional anaesthesia in paediatric practice. *Canadian Journal of Anaesthesia* 1987; **34**: S43–S48.
44. Yaster M, Maxwell LG. Pediatric regional anaesthesia. *Anesthesiology* 1989; **70**: 324–338.

British Journal of Anaesthesia 1996; **76**: 816–821

Surgical pain is followed not only by spinal sensitization but also by supraspinal antinociception

O. H. G. WILDER-SMITH, E. TASSONYI, C. SENLY, PH. OTTEN AND L. ARENDT-NIELSEN

Summary

Nociception can produce segmental spinal sensitization or descending supraspinal antinociception. We assessed both types of sensory change after surgery during isoflurane–nitrous oxide anaesthesia with or without fentanyl before nociception. Patients undergoing back surgery received fentanyl 3 μg kg^{-1} ($n = 15$) or placebo ($n = 15$) before anaesthesia in a prospective, randomized, blinded study. Sensation, pain detection and tolerance thresholds to electrical stimulation were measured before operation at the arm, incision and herniated disc dermatomes (HDD) and 1, 2, 4, 6, 24 h and 5 days after operation, together with pain scores and patient-controlled morphine consumption (duration 24 h). For segmental effects, thresholds were normalized to the thresholds at a distant dermatome (arm). Raw pain thresholds were increased after operation (fentanyl > placebo) and were maximal at 4 h (pain tolerance in HDD: fentanyl +5.2 mA (+62.7%), placebo, +3.8 mA (+44.2%); $P < 0.05$ *vs* baseline for both). Normalized sensation thresholds decreased for placebo only (HDD/4 h: placebo, −1.8 (−44.8%), $P < 0.05$; fentanyl, +0.1 (+5.5%) ns). All changes returned to baseline by 24 h except for the placebo group normalized HDD sensation (d5: placebo, −2.4 (−59.7)%, $P < 0.05$; fentanyl −0.1 (−5.5%) ns). Pain scores and morphine consumption were similar. The study demonstrated both supraspinal analgesia and spinal sensitization after surgery. Fentanyl administration before operation augmented the former while decreasing the latter, and hence sensitization, especially if neuropathic, may particularly benefit from pre-emptive analgesia. (*Br. J. Anaesth.* 1996; **76**: 816–821)

Key words
Pain, postoperative. Analgesia, postoperative. Analgesia, pre-emptive. Pain, threshold.

In an editorial discussing pain after surgery, Wall [1] noted, on the basis of animal experimentation, that nociception results in excitatory, segmental changes in central, spinal sensory processing (spinal sensitization). In animal experiments, it was found not only that opioids depress spinal sensitization, but that they were considerably more effective if given before rather than after nociception (pre-emptive analgesia) [2]. The clinical application of these findings has generated considerable debate, with the clinical reality of pre-emptive analgesia remaining controversial and the subject of intensive investigation [3, 4]. In particular, it has proved difficult to demonstrate clinically significant effects on analgesic consumption and clinical pain measures [3, 4].

Groups [5, 6] working on intact animals and with more intense nociceptive stressors described opposing, inhibitory and supraspinal phenomena, such as "stress-induced analgesia (SIA)" or "diffuse noxious inhibitory controls (DNIC)". These groups used nociception that was longer-lasting or more intense, or both, than that of spinal sensitization models (e.g. being forced to swim in hot water *vs* short-lasting electrical stimulation), and found analgesia and hyposensitivity in sensory testing afterwards [7]. Similar sensory inhibition was elicited by stimulation of various brain regions ("stimulation-induced analgesia") [6]. SIA operates via descending, inhibitory encephalinergic, α-adrenergic and NMDA systems [8].

Whether human surgery is associated with spinal sensitization or supraspinal inhibition has not been investigated in detail. Only few studies have examined the effect of pre-emptive analgesia on spinal sensitization; we have found none for SIA or DNIC. Richmond, Bromley and Woolf [9] and Collis and colleagues [10] found that mechanical secondary hyperalgesia was suppressed by pre-emptive morphine, but they did not give absolute thresholds. On a single occasion after operation, Lund, Hansen and Kehlet found an increased electric sensation threshold [11], while electric pain thresholds were decreased (and the nociceptive withdrawal reflex increased) in another study [12]. Both Willer, Bergeret and Gaudy [13] and Peters and colleagues [14] found increased thresholds in small postoperative studies. Thus data on postoperative changes in sensory processing with human surgery are scarce and contradictory.

The aim of this study was to investigate sensory processing after surgery using sensory skin thresholds. In particular, we were interested in

---

O. H. G. WILDER-SMITH, MB, CHB, MD, E. TASSONYI, MD, DSC, C. SENLY, MD (Department of Anaesthesiology); PH. OTTEN, MD (Department of Neurosurgery); Geneva University Hospital, 24 rue Micheli-du-Crest, CH-1211 Geneva 14, Switzerland. L. ARENDT-NIELSEN, PHD, Centre for Sensory-Motor Interaction, Laboratory for Experimental Pain Research, University of Aalborg, Fredrik Bajersvej 7D, DK-9220 Aalborg E, Denmark.
Accepted for publication: February 7, 1996.
Correspondence to O.H.G.W.-S.

detecting and differentiating between generalized (e.g. supraspinal inhibition) and segmental (e.g. spinal sensitization) changes in sensory function. We also determined the effect of pre-emptive fentanyl analgesia on changes in sensory processing which might be present after surgery. Finally, we determined if altered sensory processing affects clinical measures of pain (analgesic consumption, pain scores).

Patients and methods

We studied 30 ASA I and II patients, undergoing elective herniated intervertebral disc surgery. The study design was prospective, randomized and double-blind. Institutional review board and Ethics Committee approval were obtained, and all patients gave informed written consent.

Patients were instructed on threshold measurement, pain verbal rating scores (VRS) and use of a patient-controlled analgesia (PCA) pump. They received no premedication on the morning of operation. Before insertion of a venous cannula, pain verbal rating scores (0 = no pain; 10 = worst pain imaginable) for the back and affected leg dermatome and sensation, pain detection and pain tolerance thresholds were determined. Thresholds were obtained using constant skin current stimulation (Digistim, Biometer A/S, Copenhagen/DK; tetanic stimulation at 100 Hz, 0.2 ms square wave pulses) via self-adhesive electrodes 3 cm apart. Measurements were carried out in the middle of the nerve root dermatome most affected by disc prolapse; on the flanks at the height of the back incision (T12–L1 dermatome), ipsilateral and contralateral to the side of the involved nerve root; and the proximal arm contralateral to the involved nerve root (C8–T1). Care was taken not to stimulate major nerves, and measurements were separated by 5 min. The three end-points, measured successively in a run, were the averages of the three runs.

Five minutes before induction of anaesthesia, patients received a blinded short infusion (0.9 % NaCL 100 ml) containing either placebo (placebo group) or fentanyl 3 $\mu g\ kg^{-1}$ (fentanyl group). Anaesthesia was induced with thiopentone 5 $mg\ kg^{-1}$, followed by vecuronium 0.1 $mg\ kg^{-1}$. After tracheal intubation, anaesthesia was maintained with isoflurane and 66 % nitrous oxide in oxygen. No other supplementation was given and the interventions usually lasted less than 1 h.

Thirty minutes after extubation, morphine by patient-controlled analgesia (PCA) was started (loading bolus 60 $\mu g\ kg^{-1}$, PCA bolus 25 $\mu g\ kg^{-1}$; lock-out interval 8 min in recovery room, 15 min on ward; background infusion 15 $\mu g\ kg^{-1}\ h^{-1}$ during the first 2 h in the recovery room). No other analgesics were given. Threshold and VRS measures, as before, and cumulative morphine consumption were assessed 1, 2, 4, 6 and 24 h after extubation. PCA morphine was discontinued 24 h after operation. Threshold and VRS values were obtained 5 days after operation. Observer sedation rating scores (5 = wide awake, 1 = unrousable) were also noted at measurement times.

Based on the data of Lautenbacher and Rollman [15], the study was designed to have the power to detect a difference of 20 % in sensation thresholds. To separate generalized from segmental (spinal) effects on thresholds, normalized (or relative) and raw thresholds were analysed. Thresholds were normalized relative to the arm [9, 10]. Thus normalized thresholds were calculated by dividing para-incisional and affected dermatome threshold values by the respective arm threshold values. All statistical analysis was performed using the software package Statistica for Windows (release 4.5, Statsoft Inc, 2325 East 13th Street, Tulsa, OK 74104, USA). Patient data were compared by unpaired *t* test. Analysis of thresholds, pain VRS or sedation scores and cumulative morphine consumption was by repeated measures ANCOVA, with the preoperative baseline values acting as covariant. *Post hoc* testing was by Tukey's honest significant difference test. Statistical significance was assumed if $P < 0.05$.

Results

The two groups were comparable (table 1), with similar preoperative (baseline) pain VRS and threshold values. There were no significant differences between groups for back or leg pain VRS, cumulative morphine consumption or observer sedation scores (table 2).

Raw thresholds were increased after operation (table 3, fig. 1). In both groups mainly the 4-h measurements of affected dermatome pain thresholds were increased significantly compared with baseline. Combining all thresholds, the fentanyl group values were significantly higher than the placebo values ($P < 0.02$). Overall, the thresholds at different measurement sites and the sensation, pain detection and pain tolerance thresholds were significantly different ($P < 0.008$ and 0.00001, respectively). Arm site thresholds overall were significantly lower than for the para-incisional site ($P < 0.024$), with no significant difference between para-incisional and affected dermatome thresholds. All three threshold test types differed from each other ($P < 0.0001$). For thresholds overall, values at 24 h and 5 days were generally lower than the preceding postoperative values ($P < 0.0001$). Baseline thresholds significantly affected subsequent values ($P < 0.0001$).

For normalized thresholds taken together (fig. 2), the groups or measurement sites did not differ. Only in the placebo group were sensation thresholds in the affected dermatome significantly lower than baseline at 4 and 6 h and 5 days after operation. Overall, the three threshold test types continued to be different ($P < 0.00001$), and day 5 threshold values together differed from those at 1, 2 and 24 h after operation. For sensation thresholds alone, the values in the placebo group were significantly lower than in the fentanyl group ($P < 0.003$) overall. Baseline values

Table 1 Patient data (mean (SD or range))

	Age (yr)	Weight (kg)	Height (cm)	Sex (M:F)
Placebo	47.8 (24–64)	75.0 (13.4)	171.9 (9.2)	10:5
Fentanyl	41.1 (27–62)	74.3 (14.6)	169.5 (20.6)	12:3

Table 2 Pain, sedation and morphine consumption. VRS = Verbal rating score for leg (L) or back (B) pain; OSS = observer sedation score; morphine = cumulative morphine consumption. Values for VRS and OSS are median (quartile range); cumulative morphine consumption values are mean (SD). BL = Baseline.

	Time after operation						
	BL	1 h	2 h	4 h	6 h	24 h	5 days
VRS/L							
Placebo	0 (0–2.5)	2 (0–4)	2 (0–3.5)	1 (0–4.5)	0 (0–1.5)	1 (0–1.5)	0.5 (0–2.0)
Fentanyl	1 (0–2.5)	2 (1–3.5)	0 (0–1.5)	0 (0–1.5)	0 (0–2.5)	0 (0–2)	2 (0–3)
VRS/B							
Placebo	0 (0–0.5)	5 (2.5–5.5)	3 (2–4)	4 (2–5)	2.5 (0.5–3)	2.5 (1–3.5)	1 (0.5–1)
Fentanyl	0 (0–1)	4 (1.5–5.5)	3 (1.5–4.5)	3 (1.5–4.5)	3 (0–4)	1 (0–2.5)	1 (0–2)
OSS							
Placebo	5 (5–5)	4 (3–4)	4 (4–5)	5 (5–5)	5 (4–5)	5 (5–5)	5 (5–5)
Fentanyl	5 (5–5)	4 (3–4)	4 (4–4.5)	5 (4–5)	5 (4–5)	5 (5–5)	5 (5–5)
Morphine (mg)							
Placebo	0	6.3 (2.3)	9.8 (4.1)	15.3 (6.2)	18.5 (7.2)	33.7 (13.5)	
Fentanyl	0	6.4 (1.7)	10.3 (5.3)	16.8 (9.2)	21.1 (12.4)	38.0 (29.8)	

Table 3 Absolute threshold values. Values are (mean (SD)) mA, times (except control) are postoperative. C = Incision dermatome contralateral to affected side, I = incision dermatome ipsilateral to affected side, D = dermatome affected most by nerve compression caused by disc prolapse. *$P < 0.05$ *vs* baseline; †$P < 0.05$ *vs* day 5 value. Only the differences at individual times for a given threshold type and dermatome are marked; for other results, see text.

		Time after operation					
	Control	1 h	2 h	4 h	6 h	24 h	5 days
Sensation thresholds							
Arm, placebo	0.8 (0.7)	2.3 (2.4)	2.7 (1.7)	2.0 (1.5)	2.1 (1.4)	2.1 (1.7)	0.8 (1.1)
Arm, fentanyl	1.0 (0.9)	2.1 (1.3)	2.5 (2.2)	1.9 (1.2)	1.7 (0.9)	1.5 (1.3)	0.4 (0.5)
C, placebo	0.8 (0.5)	2.2 (1.5)	2.3 (1.6)	1.9 (1.0)	2.1 (1.3)	2.1 (1.0)	0.7 (0.8)
C, fentanyl	1.1 (0.8)	3.5 (2.4)	3.7 (1.9)	3.0 (1.9)	2.6 (2.0)	2.9 (2.8)	0.5 (0.4)
I, placebo	0.9 (0.5)	2.4 (2.1)	2.2 (1.4)	2.1 (2.1)	2.5 (1.8)	2.2 (1.1)	0.6 (0.5)
I, fentanyl	1.2 (0.8)	2.7 (2.1)	3.0 (1.7)	2.6 (1.5)	2.4 (1.2)	1.7 (1.1)	0.5 (0.4)
D, placebo	1.9 (2.1)	3.7 (2.4)	3.3 (2.7)	3.5 (2.4)	3.3 (2.5)	2.9 (2.7)	1.0 (1.3)
D, fentanyl	1.4 (1.1)	3.2 (2.4)	3.2 (2.1)	3.2 (2.8)	2.5 (1.5)	1.8 (1.4)	0.9 (0.9)
Pain detection thresholds							
Arm, placebo	5.3 (3.5)	6.4 (4.1)	6.6 (4.6)	6.2 (3.5)	5.4 (2.9)	6.3 (3.3)	2.8 (3.7)
Arm, fentanyl	4.9 (3.2)	7.9 (3.5)	8.1 (3.3)	7.0 (3.2)	6.3 (3.4)	5.6 (3.2)	3.6 (3.1)
C, placebo	5.1 (3.7)	7.3 (3.6)	7.7 (3.9)	7.5 (3.3)†	7.4 (3.8)†	7.4 (4.1)†	2.8 (2.9)
C, fentanyl	5.4 (3.1)	9.5 (4.0)	8.3 (3.2)	8.5 (3.4)	7.8 (3.8)	6.8 (4.2)	3.1 (3.5)
I, placebo	5.2 (4.0)	8.4 (5.0)†	7.9 (5.1)†	7.7 (4.9)†	7.6 (4.2)†	8.3 (4.1)†	2.6 (3.3)
I, fentanyl	6.1 (3.1)	8.0 (3.4)	9.0 (3.5)	8.0 (3.3)	8.1 (3.5)	6.2 (3.6)	2.6 (2.2)
D, placebo	5.7 (5.2)	8.0 (5.1)	7.8 (5.1)	8.5 (5.2)†	9.3 (5.2)†	6.9 (4.7)	2.9 (3.5)
D, fentanyl	4.8 (2.8)	8.4 (4.0)	8.0 (3.8)	9.6 (6.2)†‡	7.0 (3.1)	6.6 (3.0)	3.7 (3.0)
Pain tolerance thresholds							
Arm, placebo	9.7 (4.2)	11.6 (5.0)†	10.4 (5.3)	10.6 (4.3)†	10.2 (4.0)†	9.4 (3.7)	5.2 (4.4)*
Arm, fentanyl	8.9 (4.0)	12.6 (3.2)†	13.1 (3.8)†	11.7 (4.4)†	10.4 (5.1)	8.8 (3.8)	5.9 (4.6)
C, placebo	9.6 (5.1)	11.6 (3.8)†	12.2 (4.4)†	12.8 (4.4)†	12.1 (4.8)†	11.1 (4.9)†	5.4 (4.7)
C, fentanyl	9.0 (3.1)	13.9 (4.3)†	13.5 (4.1)†	14.0 (4.4)†*	13.0 (5.4)†	10.1 (5.1)†	5.6 (5.5)
I, placebo	9.3 (4.7)	11.7 (5.7)†	12.5 (5.8)†	11.6 (5.2)†	11.8 (5.0)†	12.1 (4.5)†	4.9 (4.3)
I, fentanyl	9.5 (3.4)	15.0 (5.8)†	13.7 (4.4)†	13.3 (4.3)†	13.6 (3.8)†	9.9 (4.1)	5.7 (4.8)
D, placebo	8.6 (6.0)	11.4 (5.8)†	11.4 (6.0)†	12.4 (6.3)†*	13.2 (6.2)†*	10.4 (5.7)†	5.1 (4.9)
D, fentanyl	8.3 (4.3)	12.6 (5.5)	12.6 (5.1)	13.5 (8.0)†*	11.0 (6.0)	9.6 (4.7)	7.2 (6.3)

influenced normalized thresholds only up to 4 h after operation.

Discussion

In this study, surgery was associated with generalized sensory inhibition and segmental sensitization in the immediate postoperative period. Changes in sensory processing generally returned to baseline within 24 h after operation. Compared with placebo, pre-emptive fentanyl inhibited segmental sensitization, and was accompanied by increased generalized sensory inhibition. These differences between groups were not significantly reflected in clinical measures such as pain scores or morphine consumption in our study, indicating the importance

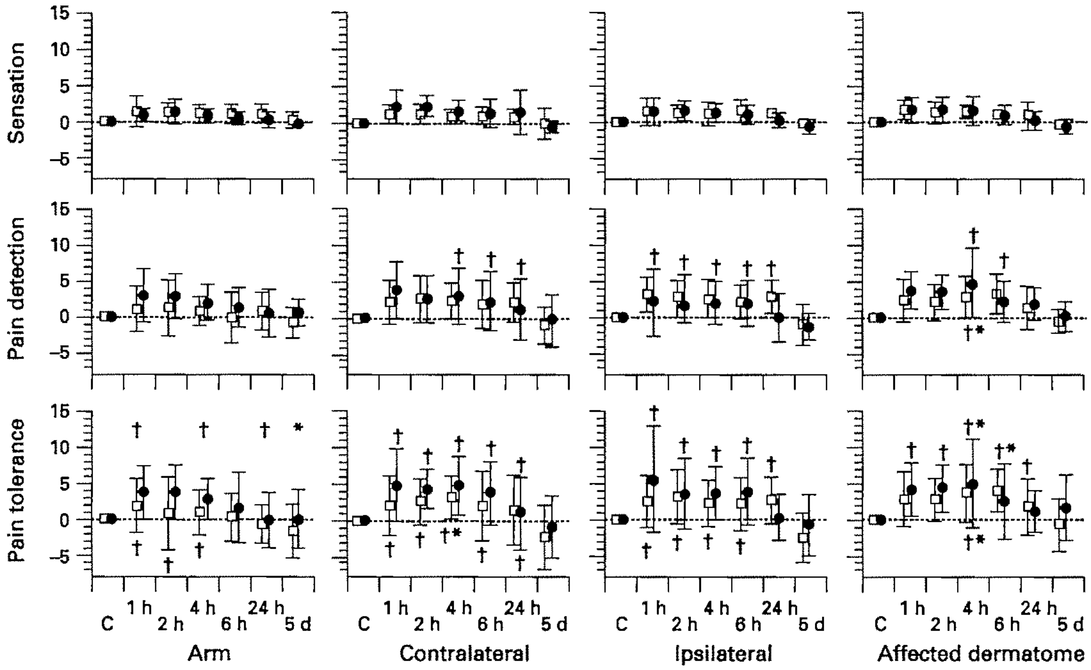


Figure 1 Changes from baseline of raw sensory thresholds (mean, SD mA). The dermatomes tested (X axis) and the types of threshold tests (Y axis) are indicated. *$P < 0.05$ *vs* baseline; †$P < 0.05$ *vs* day 5 value. The significances for the placebo group are marked above the zero line, those for the fentanyl group, below. Only differences at individual times within a given graph are marked (for other results, see text).

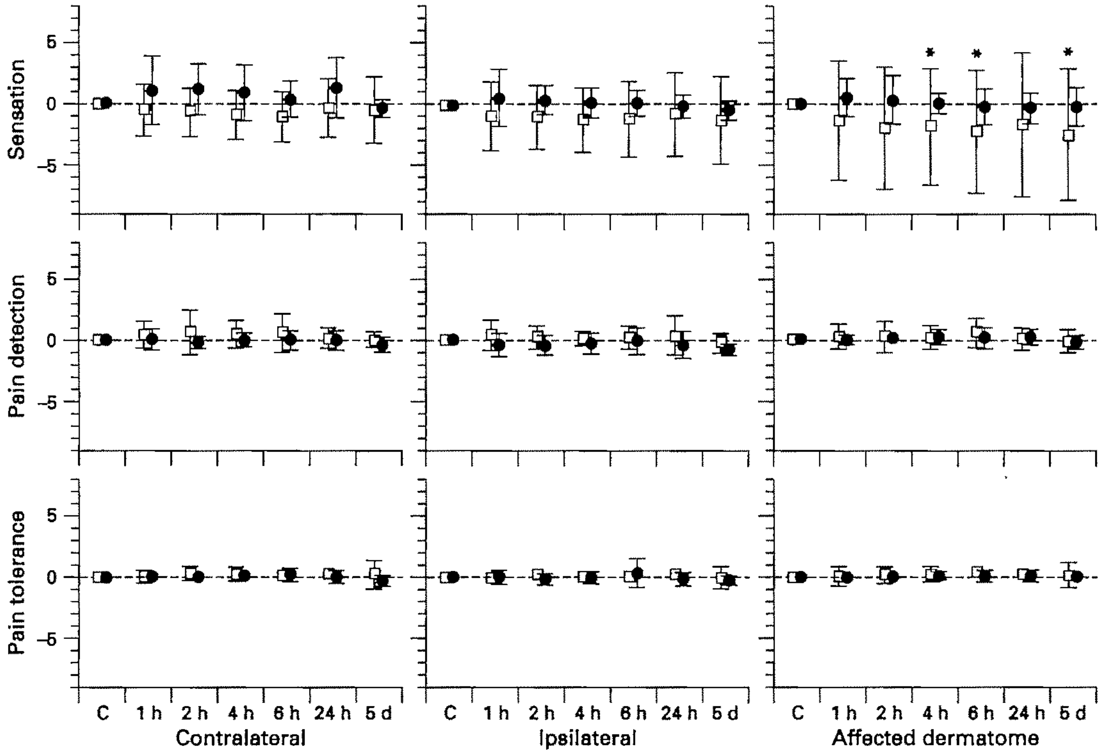


Figure 2 Changes from baseline of normalized sensory thresholds in arbitrary units (mean, SD rations). The dermatomes tested (X axis) and the types of threshold tests (Y axis) are indicated. *$P < 0.05$ *vs* baseline. The significances for the placebo group are marked above the zero line, those for the fentanyl group, below. Only differences at individual times within a given graph are marked (for other results, see text).

of sensory testing in assessing nociception after operation.

Measurement of pain thresholds by cutaneous electrical stimulation is easy to use and well validated [15]. While electrical thresholds do not represent a pure nociceptive activation, but a mixed nerve fibre population response, we consider its use acceptable in the surgical context because surgery also involves a mixed response. Additionally, use of the more complex equipment necessary for pure nociceptive stimulation (lasers, Peltier elements) is difficult if not impossible on the ward. Possible sensitization by threshold measurements was minimized by spacing the measures, doing only three runs and stopping on just reaching the pain tolerance threshold. In common with other groups [9, 10] we normalized thresholds relative to the arm. Because the arm was far away from the surgical site, it was unlikely to be affected by segmental or spinal sensory changes after operation, while still being subject to any generalized or supraspinal changes, making possible separation of the two types of altered sensory processing.

Extraneous factors which may have influenced thresholds include increased reaction times and analgesic or anaesthetic drugs. In order to decrease the effect of reaction times, electric stimulation was increased very slowly (approximately 0.1 mA s^{-1}). In addition, sedation scores were similar between groups throughout, and were normal by 4 h after operation. Isoflurane in subanaesthetic concentrations has no effect on pain detection thresholds [16]; nitrous oxide may increase pain detection thresholds for up to 30 min after its discontinuation [17]. Opioids such as morphine or fentanyl have no direct effects on sensation or pain detection thresholds [18]. The effects on pain tolerance thresholds are most visible if the stimulus is long or repeated, and are small for tolerance to single pain stimuli [18]. Thus direct drug effects on the thresholds can be expected to have been minimal, particularly with regard to sensation and pain detection thresholds.

Patients titrated themselves to similar pain levels in the groups using PCA morphine. The lack of difference in morphine consumption may primarily result from group size, or because back surgery is only moderately painful, or both. The group size had the statistical power to detect a difference of 50 % in morphine consumption at 24 h between the groups. These results suggest that sensory testing may be more sensitive in the assessment of change after operation than clinical measures such as morphine consumption or pain scores. The relevance of such sensory changes for long-term outcome needs investigation.

We have found no other studies which have systematically investigated sensory thresholds after surgery in humans with regard to spinal sensitization or supraspinal inhibition. Richmond, Bromley and Woolf [9] and Collis and colleagues [10], studying pre-emptive morphine for hysterectomy, found postoperative differential (i.e. forearm–abdomen) pain detection thresholds to mechanical stimulation to be smaller in the pre-emptive group, suggesting less spinal sensitization. There was no difference in sensation thresholds. No preoperative measures were given, however, making further interpretation difficult. The absence of threshold values in a dermatome distant to the surgical site precludes conclusions about the presence or absence of generalized sensory inhibition. The mainly raised thresholds in the studies of Lund, Hansen and Kehlet [11], Dahl and colleagues [12], Willer, Bergeret and Gaudy [13] and Peters and colleagues [14] have already been mentioned. Their results are difficult to compare with ours, as they involved different times, sites and methods.

The increased sensory thresholds after operation demonstrated in our study are likely to be the result of descending central inhibitory controls elicited by the nociception of surgery (e.g. SIA or DNIC [5–8]. Sensory inhibition in our study was generalized and detectable up to 24 h after operation. DNIC operates on convergent neurones and generally fades shortly after the conditioning stimulus [19], making it a less likely mechanism in this case than SIA. SIA is supported further by the fact that while DNIC is depressed by opioids [20], SIA has been described as being augmented by opioid supplementation [21, 22]. However, SIA mechanisms are complex, involving both opioid and non-opioid pathways, possibly mutually antagonistic [23], and a final understanding must await more complete elucidation of this phenomenon. The only possible alternative explanation could be the level adaptation theory, which postulates that pain thresholds change because of resetting of the reference point for pain thresholds [14]. This theory is unlikely to explain the shift in *sensation* thresholds also seen in our study, but definite differentiation would depend on measurement of the nociceptive withdrawal reflex [14] not performed in our study. It should however be remembered that the withdrawal reflex is affected by changes both in the sensory and motor system. Segmental spinal sensitization caused by nociception is also well described in the literature for animal models [2, 3]. Studies confirming spinal sensitization after nociception in human volunteers have now been performed [24], but formal clinical studies are still lacking, as are studies of the long-term implications of such changes for outcome after surgery.

The fentanyl supplemented group showed more supraspinal antinociception after operation than the placebo group. This would suggest that, as shown experimentally [21, 22], opioids act synergistically with descending inhibitory systems, providing another rationale for pre-emptive analgesia. Opioids are effective at preventing and treating spinal sensitization, particularly of the nociceptive system [4], as confirmed by our study. The fentanyl group showed no segmental sensitization; in the placebo group it was visible only for the somatosensory system. Expression of nociceptive system sensitization in the placebo group may have been suppressed by morphine analgesia in the context of only moderately nociceptive surgery, leaving only somatosensory sensitization visible [25]. This possibility needs further study using more painful surgical interventions and larger patient groups. In the placebo group, segmental sensitization was still present compared with the fentanyl group in the affected dermatome 5 days after operation, at a time when all other sensory changes had reverted to normal. This suggests that under special circumstances (e.g. the presence before surgery of neuropathic pain or sensitization associated with nerve damage), changes in sensory processing can persist long-term with poorly blocked pre- or intraoperative nociception, as also suggested by the amputation studies of Bach, Noreng and Tjellden [26]. Further studies are needed to confirm this.

References

1. Wall PD. The prevention of postoperative pain. *Pain* 1988; **33**: 289–290.
2. Woolf CJ, Wall PD. Morphine-sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. *Neuroscience Letters* 1986; **64**: 221–225.
3. Woolf CJ, Chong MS. Pre-emptive analgesia: treating postoperative pain by preventing the establishment of central sensitisation. *Anesthesia and Analgesia* 1993; **77**: 362–379.
4. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain* 1993; **52**: 259–285.
5. Le Bars D, Dickenson AH, Besson JC. Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. *Pain* 1979; **10**: 283–304.
6. Termann GW, Penner ER, Liebeskind JC. Stimulation-produced and stress-induced analgesia: cross-tolerance between opioid forms. *Brain Research* 1986; **372**: 167–171.
7. Kelly DD (editor). Stress-induced analgesia. *Annals of the New York Academy of Sciences* 1986; **467**: 1–449.
8. Sternberg WF, Liebeskind JC. The analgesic response to stress: genetic and gender considerations. *European Journal Anaesthesiology* 1995; **12** (Suppl. 10): 14–17.
9. Richmond CE, Bromley LM, Woolf CJ. Preoperative morphine pre-empts postoperative pain. *Lancet* 1993; **342**: 73–75.
10. Collis R, Brandner B, Bromley LM, Woolf CJ. Is there any clinical advantage of increasing the pre-emptive dose of morphine or combining pre-incisional with postoperative morphine administration? *British Journal of Anaesthesia* 1995; 74: 396–399.
11. Lund C, Hansen OB, Kehlet H. Effect of surgery on sensory threshold and somatosensory evoked potentials after skin stimulation. *British Journal of Anaesthesia* 1990; **65**: 173–176.
12. Dahl JB, Erichsen CJ, Fuglsang-Frederiksen A, Kehlet H. Pain sensation and nociceptive reflex excitability in surgical patients and human volunteers. *British Journal of Anaesthesia* 1992; **69**: 117–121.
13. Willer JC, Bergeret S, Gaudy JH. Epidural morphine strongly depresses nociceptive flexion reflexes in patients with postoperative pain. *Anesthesiology* 1985; **63**: 675–680.
14. Peters ML, Schmidt AJM, Van den Hout MA, Koopmans R, Sluijter M. Chronic back pain, acute postoperative pain and the activation of diffuse noxious inhibitory controls. *Pain* 1992; **50**: 177–187.
15. Lautenbacher S, Rollman GB. Sex differences in responsiveness to painful and non-painful stimuli are dependent upon the stimulation method. *Pain* 1993; **53**: 255–264.
16. Tomi K, Mashimoto T, Tashiro C, Yagi M, Pak M, Nishimura S, Nishimura M, Yoshiya I. Alterations in pain threshold and psychomotor response associated with subanaesthetic concentrations of inhalation anaesthetics in humans. *British Journal of Anaesthesia* 1993; **70**: 684–686.
17. Ramsay DS, Brown AC, Woods SC. Acute tolerance to nitrous oxide in humans. *Pain* 1992; **51**: 367–373.
18. van der Burght M, Rasmussen SE, Arendt-Nielsen L, Bjerring P. Morphine does not affect laser induced warmth and pin prick thresholds. *Acta Scandinavica Anaesthesiologica* 1994; **38**: 161–164.
19. Bouhassira D, Bing Z, Le Bars D. Studies of the brain structures involved in diffuse noxious inhibitory controls in the rat: the rostral ventromedial medulla. *Journal of Physiology (London)* 1993; **463**: 667–687.
20. Le Bars D, Willer JC, De Broucker T. Morphine blocks descending pain inhibitory controls in humans. *Pain* 1992; **48**: 13–20.
21. Woolfolk DR, Holtzman SG. Restraint stress potentiates analgesia induced by 5′-N-ethylcarboxamidoadenosine: comparison with morphine. *European Journal of Pharmacology* 1993; **239**: 177–182.
22. Gogas KR, Presley RW, Levine JD, Basbaum AI. The antinociceptive action of supraspinal opioids results from an increase in descending inhibitory control: correlation of nociceptive behaviour and c-fos expression. *Neuroscience* 1991; **42**: 617–628.
23. Grisel JE, Fleshner M, Watkins LR, Maier SF. Opioid and nonopioid interactions in two forms of stress-induced analgesia. *Pharmacology, Biochemistry and Behavior* 1993; **45**: 161–172.
24. Brennum, J, Dahl JB, Moiniche S, Arendt-Nielsen L. Quantitative sensory examination of epidural anaesthesia and analgesia in man: effects of pre- and post-traumatic morphine on hyperalgesia. *Pain* 1994; **59**: 261–271.
25. Herrero JF, Headley PM. Sensitization of spinal neurons by non-noxious stimuli in the awake but not anesthetized state. *Anesthesiology* 1995; **82**: 267–275.
26. Bach S, Noreng MF, Tjellden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. *Pain* 1988; **33**: 297–301.

British Journal of Anaesthesia 1996; **76**: 822–828

Haemostatic changes caused by i.v. regional anaesthesia with lignocaine

T. T. NIEMI, A. H. KUITUNEN, E. M. VAHTERA AND P. H. ROSENBERG

Summary

The various components of i.v. regional anaesthesia (IVRA), that is ischaemia, tourniquet compression and the presence of high concentrations of local anaesthetics in the blood vessels of the extremity, may affect haemostatic mechanisms. We performed a cross-over study in 10 healthy male volunteers to examine the role of lignocaine in IVRA on several haemostatic variables, and those indicating fibrinolysis and platelet function in particular. Venous blood samples were obtained from the test arm and the opposite arm before IVRA, at the time of tourniquet cuff deflation and 30 min thereafter. Metal needle punctures were used, and for the sample from the test arm at the time of cuff deflation, cuff pressure was reduced from 300 mm Hg to individual mean arterial pressure. The IVRA technique included exsanguination by arm elevation and axillary artery compression, inflation of the tourniquet cuff for 20 min and deflation of the cuff in one step (after obtaining the venous sample). Each subject received, in random order, either 0.5% lignocaine 3 mg kg^{-1} or the corresponding volume of saline i.v. All fibrinolysis markers, that is, D-dimer, tissue plasminogen activator antigen (t-PA antigen), tissue plasminogen activator activity (t-PA activity), plasminogen activator inhibitor activity (PAI) and protein C indicated enhanced fibrinolysis by IVRA, but only t-PA antigen and PAI showed greater changes in the lignocaine compared with the saline group in the exposed arm at the time of cuff deflation. Platelet function tests (ADP-induced platelet aggregation, β-thromboglobulin and thrombelastogram (TEG)) indicated no differences between the lignocaine and saline groups. Although IVRA appeared to induce some platelet dysfunction, there was a small increase in TEG amplitude indicative of improved fibrin–platelet interaction in the lignocaine-exposed arm at the time of cuff deflation. We conclude that the presence of high i.v. lignocaine concentrations (median 144.4 μg ml^{-1} in cubital veins at the end of the tourniquet time) potentiated ischaemia-induced fibrinolysis activation during IVRA. Concomitant platelet dysfunction was not aggravated by lignocaine. (*Br. J. Anaesth.* 1996; **76**: 822–828)

Key words

Blood, haemostasis. Blood, coagulation. Anaesthetic techniques, regional. Anaesthetics local, lignocaine.

I.v. regional anaesthesia (IVRA) is used widely for minor operations of the extremities. The technique includes a pneumatic tourniquet and i.v. injection of local anaesthetic distal to the tourniquet. The various components of IVRA, such as ischaemia, tourniquet compression and intravascular local anaesthetic, may affect haemostatic mechanisms. Fibrinolytic activity increases both in the occluded limb and in the systemic circulation during tourniquet ischaemia [1–3]. This activity is associated with a low incidence of deep venous thrombosis in the exposed limb [2, 3]. However, there are reports of embolic events after tourniquet release [4, 5]. Embolic material is probably derived from fresh thrombi formed during tourniquet inflation [6].

A schematic representation of fibrinolysis is shown in figure 1. Tissue plasminogen activator (t-PA) is a primary activator which converts plasminogen to plasmin. It is produced by and released continuously from the vascular endothelial cells and after some local or systemic stimuli [7]. t-PA-mediated plasminogen activation is inhibited directly by plasminogen activator inhibitors (PAI), mainly PAI-1 (fig. 1) [8].

Clinically useful thrombosis prophylaxis by i.v. lignocaine has been demonstrated [9]. Lignocaine also has an antithrombotic effect when administered topically in rat microvascular injury [10]. Local anaesthetics are known to inhibit platelet aggregation but only at much higher concentrations that may occur normally during extradural or brachial plexus block [11]. In contrast, during IVRA, local anaesthetic concentration in the isolated limb may be 50–100 times higher than that associated with other types of regional anaesthetic techniques [12].

In this study, therefore, we evaluated the role of lignocaine on platelet function and fibrinolysis during and after IVRA, without surgery.

Subjects and methods

We studied 10 apparently healthy, male, non-smoking volunteers, aged 29–50 yr, in a randomized,

---

T. T. NIEMI*, MD, A. H. KUITUNEN, MD, PHD, P. H. ROSENBERG, MD, PHD, Department of Anaesthesiology, Helsinki University Central Hospital. E. M. VAHTERA, PHIL LIC, Finnish Red Cross Blood Transfusion Service, Helsinki, Finland. Accepted for publication: February 7, 1996.

*Address for correspondence: Department of Anaesthesia, Töölö Hospital, Helsinki Central University Hospital, Topeliuksenkatu 5, FIN-00260 Helsinki, Finland.

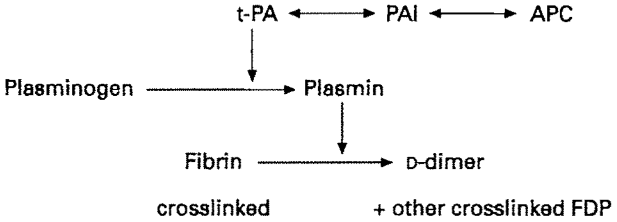


Figure 1 Schematic representation of fibrinolysis. t-PA = Tissue-type plasminogen activator, PAI = plasminogen activator inhibitor, APC = activated protein C, FDP = fibrin degradation products.

crossover study. The interval between the two experiments in one subject was at least 2 weeks. The study was approved by the Ethics Committee of Helsinki University Central Hospital and oral informed consent was obtained. Acetylsalicylic acid or other NSAID were not allowed for 1 week before the study. Individuals fasted for at least 3 h before the experiment. During the experiment subjects were in the supine position and monitored by five-lead ECG, non-invasive arterial pressure and pulse oximetry.

A vein of the dorsum of the hand was cannulated with a 20-gauge cannula (Venflon, BOC Ohmeda AB, Sweden) for administration of lignocaine or sodium chloride. Exsanguination was achieved by elevating the arm and occluding the axillar artery for 2 min so that no pulse could be detected in the periphery by a pulse oximetry. The brachial tourniquet was pressurized to and maintained inflated at 300 mm Hg for 20 min. In random order subjects were given preservative-free 0.5 % lignocaine 3 mg kg^{-1} for IVRA of the upper extremity or the same volume of 0.9 % sodium chloride. Lignocaine or sodium chloride was injected into the vein through the cannula at a rate of approximately 20 ml min^{-1}, immediately after pneumatic cuff inflation. In order to improve drug distribution and vascular filling, a small amount of physiological saline was injected immediately after lignocaine or sodium chloride (according to body weight: 3 ml for 60–69 kg, 4 ml for 70–79 kg, 5 ml for 80–89 kg and 6 ml > 90 kg). The cannula was then removed.

Blood samples were obtained from all subjects from an antecubital vein of the arm exposed to IVRA (IL = ipsilateral samples), and the contralateral arm (CL = contralateral samples) via a 20-gauge hypodermic metal needle directly into respective assay tubes. Control samples (IL-0 and CL-0) were obtained before IVRA. After 20 min of tourniquet inflation, the pneumatic cuff pressure was reduced to mean arterial pressure and a sample was immediately obtained from the first available dilated antecubital vein. This manoeuvre was necessary in order to obtain a sufficient volume of blood as rapidly as possible with a single venepuncture. As soon as the sample had been collected, the pneumatic tourniquet was released completely and a sample was obtained from the contralateral arm (CL-20). Finally, after 30 min from tourniquet release, samples (IL-50 and CL-50) from both arms were obtained with minimal stasis; an elastic, round 5-mm diameter rubber band on the brachium exerted low pressure on the skin.

ASSAYS

For assays of D-dimer, t-PA antigen, PAI and protein C, nine volumes of blood were mixed with 1 volume of trisodium citrate 0.129 mol litre^{-1}. For t-PA activity, blood collection tubes (Biopool Stabilyte tube, Umeå, Sweden) containing 0.5 ml of citrate buffer 0.5 ml litre^{-1}, pH 4.0, were used. After centrifugating at 1400 *g* for 30 min at 24 °C, plasma was aliquoted, snap-frozen and stored at −70 °C until assayed.

D-dimer was measured with an ELISA method according to the manufacturer (Asserachrom D-Di, Diagnostica Stago, Asnières, France). Expected values given by the manufacturer are < 400 ng ml^{-1} (expressed in fibrinogen equivalent units). Limits of detection (LOD) and quantitation (LOQ) for the method are 50 ng ml^{-1} and 100 ng ml^{-1}, respectively.

t-PA antigen was measured according to the manufacturer using an ELISA method (Imulyse t-PA, Biopool AB, Umeå, Sweden). The normal range at rest is 1.6–9.8 ng ml^{-1} and after 20 min of venous occlusion 22.8–83.5 ng ml^{-1} in the laboratory. t-PA activity was measured with a chromogenic method according to the manufacturer (Coaset t-PA, Chromogenix AB, Mölndal, Sweden). The range in 20 individuals at rest is 0.8–6.9 iu ml^{-1} and after 20 min of venous occlusion 21.3–128 iu ml^{-1} in the laboratory. LOD for the method is 0.1 iu ml^{-1}.

PAI activity was measured with a chromogenic method according to the manufacturer (Coatest PAI, Chromogenix AB, Mölndal, Sweden). The expected value is < 23 AU ml^{-1} and after a normal 20-min venous occlusion test < 5 AU ml^{-1} assayed in the laboratory. Because there are at least four immunologically different PAI [13] we measured functional PAI, that is PAI activity. LOD for the method is 5 AU ml^{-1}.

Protein C was measured with a chromogenic method using substrate S-2366 (Chromogenix AB, Mölndal, Sweden) and protein C-activator (American Diagnostica Inc, CT, USA). A pool of 33 normal donors was used as a standard. Reference values in the laboratory are 67–131 %.

For β-thromoboglobulin (an indicator of platelet activation and dysfunction) blood was obtained into Diatube H (Diagnostica Stago, Asnières, France). After centrifuging at 4600 *g* for 30 min at 8 °C, 33 % of the volume of the plasma supernatant, by aiming the pipette tip in the middle region of the liquid portion, was collected and stored at −70 °C until assayed. Plasma β-thromboglobulin was measured using an ELISA method according to the manufacturer (Asserachrom β-TG, Diagnostica Stago, Asnières, France). Normal values given by the manufacturer are 10–40 iu ml^{-1}. LOD for the method is 10 iu ml^{-1}.

Platelet count in whole blood and packed cell volume were measured using a Cell-Dyn 610 haematology analyser (Sequoia-Turner Corporation, CA, USA).

Platelet aggregation studies were based on the turbidometric method of Born [14]. For these studies (conducted only on samples from the arm exposed to IVRA) platelet rich plasma (PRP) was prepared by centrifuging citrate blood at 150 *g* for 10 min and platelet poor plasma (PPP) by centrifuging blood at 1400 *g* for 30 min. The platelet count of PRP was adjusted to 200×10^6 litre^{-1} with autologus PPP. Aggregation (Payton Aggregometer, USA) was induced with adenosine diphosphate and the concentration of ADP causing 50% of maximum aggregation (ADP–ED$_{50}$%) was calculated.

Thrombelastograph (TEG) tracings (Hellige Company, Freiburg, Germany) were obtained from citrate whole blood. Coagulation was initiated by adding calcium chloride to the cuvettes. TEG tracings were analysed by measuring reaction time (r), coagulation time ($r+k$), clot formation (k, α angle) and maximum amplitude (MA) [15]. Platelet aggregation measurements and TEG tracings were obtained only from the ipsilateral blood samples as equipment was available only for one sample at each sample time.

For lignocaine concentrations, plasma was stored at −70 °C until lignocaine concentrations were measured by gas chromatography [16].

STATISTICS

The Wilcoxon signed rank test was used for comparisons within groups and the Mann–Whitney *U* test for comparisons between groups. $P < 0.05$ was considered significant.

Results

PACKED CELL VOLUME AND PLATELET COUNT

There were no significant changes in packed cell volume (PCV) between samples obtained before, immediately after IVRA and 30 min thereafter. Also, there were no significant changes between groups. Therefore, no PCV-dependent corrections were made in the following results. Platelet count decreased in the saline group just after cuff deflation and 30 min thereafter compared with control values ($P < 0.05$) (table 1).

t-PA ANTIGEN, t-PA ACTIVITY, PAI

t-PA antigen in the sample at the end of IVRA was significantly higher in the lignocaine compared with the saline group ($P < 0.01$) (table 2). Thirty minutes later, values had normalized and t-PA antigen was slightly, but significantly ($P < 0.05$), lower than the control value in the saline group sample of the arm not exposed to the test. At the same time, also in the lignocaine IVRA arm, t-PA antigen was decreased significantly compared with control values ($P < 0.05$).

Compared with control values, t-PA activity in the test arm samples increased significantly in both groups after IVRA ($P < 0.01$) (table 2). Although values returned towards normal in the next 30 min, the small increase in t-PA activity in the lignocaine group was still statistically significant ($P < 0.05$). After lignocaine IVRA, t-PA activity was also increased in the contralateral arm compared with control ($P < 0.05$). There were no significant differences between groups. However, on the lignocaine exposed side, at the time of cuff deflation, there were only three t-PA antigen values and one t-PA activity value which exceeded the respective upper limit of the normal range.

PAI decreased significantly ($P < 0.01$) during IVRA in the lignocaine, but not in the saline group (table 2). There was a significant difference between the groups at the end of IVRA ($P < 0.05$). In the samples 30 min later, PAI values did not differ significantly from control values. All PAI values were within the normal range.

D-DIMER

In the lignocaine group, D-dimer concentrations increased significantly during IVRA in the sample from the exposed arm (table 2). Median concentrations of D-dimer were still higher than control values in the samples 30 min after IVRA, but this difference was not statistically significant. There was no difference between groups in the change in D-dimer.

ADP-INDUCED PLATELET AGGREGATION

In the saline group, ADP–ED$_{50}$% concentration increased significantly ($P < 0.05$) during and after IVRA (table 1). There was no significant change in the lignocaine group, and no differences between groups.

β-THROMBOGLOBULIN

β-Thromboglobulin concentration (table 1) increased significantly at the end of lignocaine IVRA in the sample from the exposed arm (median 25.6 iu ml^{-1}) compared with control values (median 19.7 iu ml^{-1}). In the saline group there were no significant changes in β-thromboglobulin concentrations. There were no significant differences between groups.

THROMBELASTOGRAPHY

In the saline group, there was a small (ns) increase in reaction (r) and coagulation ($r+k$) times after IVRA compared with control TEG. The increase in maximum amplitude (MA) was statistically significant immediately after IVRA in the lignocaine group ($P < 0.05$) while MA decreased slightly (ns) in the saline group (table 3). There were no significant differences between groups for any of the TEG variables during the test.

PROTEIN C ACTIVITY

Protein C activity (table 4) decreased significantly during lignocaine IVRA in the sample from the exposed arm (median 83%) compared with control values from the same arm (median 96%) ($P < 0.05$). Sodium chloride treatment caused an even greater decrease in protein C activity (median 63% *vs* 102%, respectively) ($P < 0.01$). There was a significant difference in protein C activity in samples immediately after IVRA between the two groups ($P < 0.01$).

Table 1 Platelet counts (PC), platelet aggregation (ADP–ED_{50}% concentrations) and β-thromboglobulin (β-TG) concentrations in ipsilateral (IL) and contralateral (CL) samples (median (range)). Significant differences ($P <$ 0.05) compared with: *IL-0 NaCl; †IL-0 lignocaine (Wilcoxon signed rank test). No significant differences between groups (Mann–Whitney U test)

	Sample	Group	PC ($\times 10^9$ litre^{-1})	ADP–ED_{50}% (μmol litre^{-1})	β-TG (iu ml^{-1})
0 min	IL-0	Lignocaine	253 (190–328)	0.6 (0.3–0.9)	19.7 (12.7–37.2)
		NaCl	260 (192–305)	0.4 (0.1–1.0)	18.0 (10.0–35.0)
	CL-0	Lignocaine			18.6 (12.4–24.5)
		NaCl			22.2 (10.7–29.5)
20 min	IL-20	Lignocaine	240 (187–301)	0.7 (0.2–1.8)	25.6 (14.1–44.5)†
		NaCl	252 (160–317)*	0.7 (0.1–1.5)*	20.9 (10.0–125.0)
	CL-20	Lignocaine	248 (184–323)		17.8 (13.5–24.7)
		NaCl	267 (185–308)		27.5 (12.8–64.0)
50 min	IL-50	Lignocaine	230 (169–311)	0.7 (0.3–1.5)	19.1 (15.8–86.0)
		NaCl	231 (199–318)*	0.7 (0.2–1.3)*	22.3 (12.0–74.0)
	CL-50	Lignocaine	256 (191–307)		21.6 (15.4–41.7)
		NaCl	268 (199–300)		23.1 (12.0–53.0)

Table 2 t-PA antigen, t-PA activity, PAI activity and D-dimer in ipsilateral (IL) and contralateral (CL) samples (median (range)). **$P <$ 0.01 compared with IL-0, †$P <$ 0.05 compared with CL-0, ‡$P <$ 0.05 compared with IL-0 (Wilcoxon signed rank test); §$P <$ 0.05, §§$P <$ 0.01 between groups (Mann–Whitney U test)

	Sample	Group	t-PA antigen (ng ml^{-1})	t-PA (iu ml^{-1})	PAI (AU ml^{-1})	D-dimer (ng ml^{-1})
0 min	IL-0	Lignocaine	3.8 (2.7–5.7)	0.5 (0.2–0.7)	6.4 (5.0–9.0)	80 (50–130)
		NaCl	3.8 (2.7–6.9)	0.5 (0.3–0.7)	5.5 (5.0–10.3)	91 (50–179)
	CL-0	Lignocaine	3.4 (2.2–5.9)	0.5 (0.1–0.8)	5.6 (5.0–9.9)	80 (60–138)
		NaCl	3.8 (2.8–7.8)	0.5 (0.3–0.8)	5.0 (5.0–11.2)	86 (50–197)
20 min	IL-20	Lignocaine	7.1 (3.5–13.8)**§§	2.1 (0.7–11.5)**	5.0 (5.0–6.7)‡§	193 (60–880)**
		NaCl	3.5 (1.7–7.8)§§	1.4 (0.8–2.3)**	5.3 (5.0–7.9)§	138 (50–275)
	CL-20	Lignocaine	3.4 (2.4–5.4)	0.6 (0.3–0.8)†	5.7 (5.0–8.3)	70 (60–142)
		NaCl	3.7 (3.0–7.4)	0.6 (0.4–0.8)	5.1 (5.0–11.6)	99 (60–159)
50 min	IL-50	Lignocaine	3.4 (1.2–4.8)‡	0.6 (0.3–0.8)‡	5.0 (5.0–10.2)	111 (60–356)
		NaCl	3.6 (2.5–6.4)	0.6 (0.3–0.8)	5.7 (5.0–9.9)	127 (50–307)
	CL-50	Lignocaine	3.4 (2.3–5.4)	0.6 (0.3–0.8)	5.3 (5.0–8.5)	80 (60–158)
		NaCl	3.4 (2.8–7.3)†	0.6 (0.3–0.8)	5.8 (5.0–11.1)	95 (60–630)

Table 3 Data from thrombelastograph tracing from ipsilateral (IL) samples. r = Reaction time, k = coagulation time, k and α angle = clot formation rate, MA = maximal amplitude (median (range)). *$P <$ 0.05 compared with IL-0 lignocaine (Wilcoxon signed rank test); †$P <$ 0.05 between groups (Mann–Whitney U test)

	Sample	Group	r (min)	k (min)	$r+k$ (min)	α (°)	MA (mm)
0 min	IL-0	Lignocaine	11.5 (3.0–18.0)	7.3 (4.0–9.5)	18.8 (7.5–22.5)	32 (26–48)†	41 (36–48)
		NaCl	6.5 (3.0–16.0)	5.8 (3.5–8.0)	13.8 (7.0–23.0)	41 (30–50)†	45 (36–51)
20 min	IL-20	Lignocaine	10.8 (5.0–17.0)	6.5 (4.0–8.5)	17.8 (9.0–23.5)	36 (28–49)	46 (39–54)*
		NaCl	8.3 (5.0–15.5)	6.0 (4.0–11.5)	15.0 (9.0–24.0)	38 (29–50)	43 (36–47)
50 min	IL-50	Lignocaine	9.0 (5.0–12.5)	6.3 (5.0–11.0)	14.8 (10.0–23.5)	35 (22–45)	48 (37–52)
		NaCl	8.5 (5.5–11.0)	6.5 (5.0–9.0)	15.5 (11.0–18.5)	38 (29–43)	43 (34–49)

Table 4 Protein C activity in ipsilateral (IL) and contralateral (CL) samples (median (range)). $^{*}P < 0.05$ compared with IL-0 lignocaine, $^{**}P < 0.01$ compared with IL-0 NaCl (Wilcoxon signed rank test); $^{\dagger\dagger}P < 0.01$ between groups (Mann–Whitney *U* test)

Time	Sample	Group	Protein C (%)
0 min	IL-0	Lignocaine	96 (79–112)
		NaCl	102 (81–123)
	CL-0	Lignocaine	97 (77–110)
		NaCl	98 (76–116)
20 min	IL-20	Lignocaine	83 (58–112)*††
		NaCl	63 (27–83)**††
	CL-20	Lignocaine	95 (76–115)
		NaCl	99 (76–113)
50 min	IL-50	Lignocaine	94 (72–121)
		NaCl	98 (76–117)
	CL-50	Lignocaine	96 (72–119)
		NaCl	96 (76–119)

Table 5 Lignocaine concentrations in ipsilateral (IL) and contralateral (CL) samples (median (range))

	Sample	Lignocaine concn (μg ml^{-1})
20 min	IL-20	144.4 (25.8–246.4)
	CL-20	1.7 (0.2–2.4)
50 min	IL-50	18.7 (4.3–28.9)
	CL-50	0.9 (0.7–1.4)

ARTERIAL PRESSURE AND HEART RATE

There were no significant changes in systolic and diastolic arterial pressures before the test and immediately before tourniquet cuff deflation. Thirty minutes after saline IVRA, median diastolic pressure decreased to a value slightly below the control level ($P < 0.05$). Heart rate was stable (range 50–70 beat min^{-1} during lignocaine IVRA and 55–80 beat min^{-1} during saline IVRA), except in one volunteer who, during lignocaine IVRA, developed a transient (about 5 min) sinus tachycardia. However, his haemostatic data did not deviate from those of the others.

LIGNOCAINE PLASMA CONCENTRATIONS

Lignocaine concentrations were high (maximum 246.4 μg ml^{-1}) in the samples obtained from the exposed arm at the end of the tourniquet time (table 5). Seven of the 10 volunteers experienced symptoms of mild central nervous system toxicity (i.e. auditory disturbances, dizziness, lightheadedness) for 2–5 min after deflation of the tourniquet cuff. Thirty minutes after deflation, plasma concentrations of the exposed arm were still higher than those of the contralateral arm.

Discussion

The results of the study confirmed that fibrinolysis was activated in a limb isolated by a tourniquet [2, 3]. The presence of high i.v. concentrations of lignocaine in the ischaemic limb appeared to enhance further the fibrinolytic response, as indicated by changes in t-PA antigen and PAI. At the end of the experiment there were slightly increased t-PA activity values in the lignocaine exposed arm. At the same time t-PA antigen was decreased slightly which may have been because of rapid clearance by the liver [17].

The decrease in PAI activity by lignocaine IVRA was probably a consequence of complex formation between PAI and t-PA. This decrease in PAI is, in fact, a more logical result than the previous opposite finding of increased PAI associated with application of a tourniquet [3]. Complex formation between PAI and protein C [18] also contributes to low PAI values.

Protein C is a liver-derived glycoprotein that can neutralize PAI-1 and thus has a profibrinolytic effect [8]. When added to human and bovine endothelial cell cultures, activated protein C causes a decrease in the activity of PAI [18, 19]. The fact that PAI activity decreased more in the lignocaine group and protein C (test arm) decreased more in the saline group suggests that the effect of lignocaine is related mainly to the stimulation of t-PA release.

In blood samples from the contralateral arm there was no clear evidence of systematically enhanced fibrinolysis; a single index was the increase in t-PA activity in the sample from the contralateral arm after deflation of the tourniquet cuff. Also, in samples from the lignocaine exposed arm, 30 min after deflation, t-PA activity was still increased slightly when other fibrinolytic indicators had returned to near baseline. The results suggest short-lived enhanced regional fibrinolytic activity in the arm exposed to IVRA. Thus possible endothelial damage induced by a combination of ischaemia and high concentrations of local anaesthetic [20] does not result in any clear prolonged activation and release of fibrinolytic factors, which are known to originate in vascular endothelium [7].

Increased fibrinolytic activity is often associated with platelet dysfunction [21, 22]. Impaired platelet function was demonstrated by increased ADP-ED_{50}% concentration after IVRA with sodium chloride. A similar change was also seen after IVRA with lignocaine (median values after IVRA were almost identical), but because of greater variations between individuals, the change after lignocaine IVRA was not statistically significant.

PCV remained almost unchanged during the study. Although platelet counts showed a minimal decrease in the saline group they remained within the normal range. During IVRA, that is before tourniquet cuff deflation, venous blood in the isolated limb was diluted markedly by the added test solution (in pilot experiments, $n = 4$, median platelet count 83 (range 1–131) $\times 10^9$ litre^{-1}, median PCV 0.10 (range 0.09–0.19)). Our experimental design included releasing the cuff to a value equivalent to mean arterial pressure and thus the sampling veins in the antecubital region became filled with blood of normal PCV and normal platelet count. In this situation haemoconcentration may occur because of venous congestion which causes leakage of fluid into the extravascular space and compensates for the haemodilution effect on platelet count and PCV values. In addition to the potent fibrinolytic response (by ischaemia), dilution of blood during IVRA also contributes to prevention of coagulation in the tourniquet-isolated limb.

β-Thromboglobulin, an indicator of platelet activation and dysfunction [23], was also increased in the lignocaine group ($P < 0.05$) immediately after IVRA in samples from the exposed arm. Values remained above control, in some cases until 30 min, suggesting platelet dysfunction induced by contact of blood with the ischaemia-stressed veins. β-Thromboglobulin concentrations in the contralateral arm 30 min after IVRA were similar to baseline values indicating normal function of the majority of circulating platelets.

Interestingly, the amplitude of the TEG tracing was slightly, but significantly, increased in the lignocaine group samples of the exposed arm. In contrast with platelet dysfunction, this TEG finding suggests a stronger clot strength, that is greater fibrin–platelet interaction [15]. This change, compared with baseline, may be caused by lignocaine because *in vitro*, lignocaine has an inhibitory effect on endothelial cell-dependent antiaggregation of platelets [24].

Clinical concentrations of lignocaine (for example 2.5–4 $\mu g\ ml^{-1}$ in the circulation) are known to prevent the formation of deep vein thrombosis [11]. This beneficial effect is probably caused primarily by prevention of leucocyte adhesion, and prevention of transendothelial migration [25, 26]. In this study, resembling the clinical situation, venous lignocaine concentrations were large enough to cause local toxicity, including endothelial damage [20].

The function of platelets would also be expected to be inhibited because of the toxic actions of lignocaine [27]. Lignocaine concentrations of 10–25 $\mu g\ ml^{-1}$ inhibit platelet aggregation [28], which can be considered beneficial for the prevention of clot formation. In this study, venous concentrations in samples from the non-exposed arm were lower and thus a systemic platelet aggregation-inhibiting effect was not expected.

The neuroendocrine response to surgery has been shown to enhance haemostatic function [29], including decreased fibrinolysis [30] and increased platelet reactivity [31]. By excluding surgery and infusing stress hormones (adrenaline, cortisol and glucagon) to volunteers, Rosenfeld and colleagues [32] showed an increase in fibrinogen concentration and platelet aggregation. The haemodynamic responses to IVRA in volunteers were modest as tourniquet time was relatively short. Clinically, hypertension caused by tourniquet pain usually does not develop until after 1 h [33], but the increase in arterial pressure seems to be unrelated to changes in catecholamine or cortisol concentrations in plasma [34]. Even in those seven volunteers who developed symptoms of central nervous system toxicity, circulatory and haemostatic variables did not indicate stress.

In summary, our results confirmed that fibrinolysis was activated in a limb isolated by a tourniquet. The presence of high i.v. concentrations of lignocaine in the ischaemic limb appeared to enhance further the fibrinolytic response, as indicated by changes in t-PA antigen and PAI. The tourniquet ischaemia-induced platelet dysfunction was not enhanced by lignocaine.

Acknowledgements

We thank Professor G. Myllylä, Finnish Red Cross Transfusion Service, for assistance in the planning of this study.

References

1. Klenerman L, Mackie I, Chakrabarti R, Brozovic M, Stirling Y. Changes in haemostatic system after application of a tourniquet. *Lancet* 1977; 7: 970–972.
2. Fahmy NR, Patel DG. Hemostatic changes and postoperative deep-venous thrombosis associated with use of a pneumatic tourniquet. *Journal of Bone and Joint Surgery* 1981; **63-A**: 461–465.
3. Petäjä J, Myllynen P, Myllylä G, Vahtera E. Fibrinolysis after application of a pneumatic tourniquet. *Acta Chirurgica Scandinavica* 1987; **153**: 647–651.
4. Cohen JD, Keslin JS, Nili M, Yosipovitch Z, Gassner S. Massive pulmonary embolism and tourniquet deflation. *Anesthesia and Analgesia* 1994; **79**: 583–585.
5. Parmet JL, Berman AT, Horrow JC, Harding S, Rosenberg H. Thromboembolism coincident with tourniquet deflation during total knee arthroplasty. *Lancet* 1993; **341**: 1057–1058.
6. Parmet JL, Horrow JC, Singer R, Berman AT, Rosenberg H. Echogenic emboli upon tourniquet release during total knee arthroplasty: pulmonary hemodynamic changes and embolic composition. *Anesthesia and Analgesia* 1994; **79**: 940–945.
7. Wiman B, Hamsten A. The fibrinolytic enzyme system and its role in the aetiology of thromboembolic disease. *Seminars in Thrombosis and Haemostasis* 1990; **16**: 207–216.
8. Krishnamurti C, Alving BM. Plasminogen activator inhibitor type 1: biochemistry and evidence for modulation of fibrinolysis in vivo. *Seminars in Thrombosis and Haemostasis* 1992; **18**: 67–78.
9. Cooke ED, Bowcock SA, Lloyd MJ, Pilcher MF. Intravenous lignocaine in prevention of deep venous thrombosis after elective hip surgery. *Lancet* 1977; **15**: 797–799.
10. Luostarinen V, Evers H, Lyytikäinen MT, Scheinin A, Wahlen A. Antithrombotic effects of lignocaine and related compounds on laser-induced microvascular injury. *Acta Anaesthesiologica Scandinavica* 1981; **25**: 9–11.
11. Gibbs NM. The effect of anaesthetic agents on platelet function. *Anaesthesia and Intensive Care* 1991; **19**: 495–520.
12. Kalso EA, Lalla ML, Rosenberg PH, Tuominen MK, Santavirta S, Gribenberg J. Evaluation of the myotoxicity of bupivacaine in Bier blocks—a biochemical and electron microscopic study. *Anesthesia and Analgesia* 1983; **62**: 796–801.
13. Collen D. Report of the meeting of the subcommittee on fibrinolysis, Jerusalem, Israel, June 2, 1986 (International Committee Communications). *Thrombosis and Haemostasis* 1986; **56**: 415–416.
14. Born GVR. Quantitative investigations into the aggregation of blood platelets. *Journal of Physiology (London)* 1962; **162**: 67–71.
15. Mallet SV, Cox JA. Thrombelastography. *British Journal of Anaesthesia* 1992; **69**: 307–313.
16. Mather LE, Tucker GT. Meperidine and other basic drugs: general method for their determination in plasma. *Journal of Pharmaceutical Sciences* 1974; **63**: 306–307.

17. Nilsson T, Wallen P, Mellbring G. In vivo metabolism of human tissue-type plasminogen activator. *Scandinavian Journal of Haematology* 1984; **33**: 49–53.
18. Sakata Y, Curriden S, Lawrence D, Griffin JH, Loskutoff DJ. Activated protein C stimulates the fibrinolytic activity of cultured endothelial cells and decreases antiactivator activity. *Proceedings of the National Academy of Sciences USA* 1985; **82**: 1121–1125.
19. Himsbergh VWM, Bertina RM, Wijngarden A, Tilburg NH, Emeis JJ, Haverkate F. Activated protein C decreases plasminogen activator-inhibitor activity in endothelial cell-conditioned medium. *Blood* 1985; **65**: 444–451.
20. Suzuki N, Pitkänen M, Sariola H, Palas T, Rosenberg PH. The effect of plain 0.5% 2-chloroprocaine on venous endothelium after intravenous regional anaesthesia in the rabbit. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 653–656.
21. Bick RL. The clinical significance of fibrinogen degradation products. *Seminars in Thrombosis and Haemostasis* 1982; **8**: 302.
22. Holloway DS, Summaria L, Sandesara J, Vagher JP, Alexander JC, Caprini JA. Decreased platelet number and function and increased fibrinolysis contribute to postoperative bleeding in cardiopulmonary bypass patients. *Thrombosis and Haemostasis* 1988; **59**: 62–67.
23. Zahavi J, Kakkar VV. Beta-thromboglobulin—a specific marker of in vivo platelet release reaction. *Thrombosis and Haemostasis* 1980; **44**: 23–29.
24. Az-ma T, Yuge O. Inhibitory effect of lignocaine on cultured porcine aortic endothelial cell-dependent antiaggregation of platelets. *Anesthesiology* 1995; **83**: 374–381.
25. Hammer R, Dahlgren C, Stendahl O. Inhibition of human leucocyte metabolism and random mobility by local anaesthesia. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 520–523.
26. Eriksson AS, Sinclair R, Cassuto J, Thomsen P. Influence of lignocaine on leukocyte function in the surgical wound. *Anesthesiology* 1992; **77**: 74–78.
27. Cazenava J-P, Benveniste J, Mustard JF. Aggregation of rabbit platelets by platelet-activating factor is independent of the release reaction and the arachidonate pathway and inhibited by membrane-active drugs. *Laboratory Investigation* 1979; **41**: 275–285.
28. Borg T, Modig J. Potential anti-thrombotic effects of local anaesthetics due to their inhibition of platelet aggregation. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 739–742.
29. Konkle BA, Schuster SJ, Kelly MD, Harjes K, Hassett DE, Bohrer M, Tavassoli M. Plasminogen activator inhibitor-1 messenger RNA expression is induced in rat hepatocytes in vivo by dexamethasone. *Blood* 1992; **79**: 2636–2642.
30. Aillaud MF, Juhan-Vague I, Alessi MC, Marecal M, Vinson MF, Arnaud C, Vague P, Collen D. Increased PA-inhibitor levels in the postoperative period: No cause–effect relation with increased cortisol. *Thrombosis and Haemostasis* 1985; **54**: 466–468.
31. Rosenfeld BA, Faraday N, Campbell D, Dorman T, Clarkson K, Siedler A, Breslow MJ, Bell W. Perioperative platelet reactivity and effects of clonidine. *Anesthesiology* 1993; **79**: 255–261.
32. Rosenfeld BA, Faraday N, Campbell D, Dise K, Bell W, Goldschmidt P. Hemostatic effects of stress hormone infusion. *Anesthesiology* 1994; **81**: 1116–1126.
33. Valli H, Rosenberg PH, Kyttä J, Nurminen M. Arterial hypertension associated with the use of a tourniquet with either general or regional anaesthesia. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 279–283.
34. Rocco AG, Concepcion MA, Desai S, Dhingra U, Murray M. The effect of general and regional anesthesia on tourniquet-induced blood pressure elevation. *Regional Anesthesia* 1987; **12**: 174–180.

British Journal of Anaesthesia 1996; **76**: 829–834

Effect of systemic *N*-methyl-D-aspartate receptor antagonist (ketamine) on primary and secondary hyperalgesia in humans

S. ILKJAER, K. L. PETERSEN, J. BRENNUM, M. WERNBERG AND J. B. DAHL

Summary

Ketamine reduces nociception by binding non-competitively to the *N*-methyl-D-aspartate (NMDA) receptor, activation of which increases spinal hypersensitivity. We studied 19 healthy, unmedicated male volunteers, aged 20–31 yr. Burn injuries were produced on the medial surface of the dominant calf with a 25 × 50 mm rectangular thermode. On 3 separate days, at least 1 week apart, subjects received a bolus of either ketamine 0.15 mg kg^{-1}, ketamine 0.30 mg kg^{-1} or placebo, delivered by a mechanical infusion pump over 15 min. The bolus was followed by continuous infusion of ketamine 0.15 mg kg^{-1} h^{-1}, ketamine 0.30 mg kg^{-1} h^{-1} or placebo, respectively, for 135 min. Ketamine reduced the magnitude of both primary and secondary hyperalgesia, and also pain evoked by prolonged noxious heat stimulation, in a dose-dependent manner. In contrast, ketamine did not alter phasic heat pain perception (perception of transient, painful, thermal stimuli) in undamaged skin. The analgesic effects of ketamine in the burn injury model are in agreement with results from experimental studies, and can be distinguished from those of local anaesthetics and opioids. Side effects caused by continuous infusion of ketamine 0.15 and 0.30 mg kg^{-1} h^{-1} were frequent but clinically acceptable. (*Br. J. Anaesth.* 1996; **76**: 829–834)

Key words

Anaesthetics i.v., ketamine. Pain, mechanism. Pain, postoperative. Burns.

Peripheral tissue damage results in sensitization of dorsal horn neurones. One consequence is altered processing of afferent activity evoked by innocuous in addition to noxious stimuli, which is manifested clinically as allodynia (pain caused by a stimulus that does not normally provoke pain) and hyperalgesia (increased response to a stimulus that is normally painful) [1]. Injury-induced sensitization of dorsal horn neurones has been implicated as an important contributor to both acute and some chronic pain states [2]. In recent years the role of excitatory amino acids in nociception has been highlighted [3]. Glutamate and aspartate participate in the activation of nociceptive dorsal horn neurones as agonists for the *N*-methyl-D-aspartate (NMDA) receptor. There is substantial evidence that this receptor plays a significant role in spinal hypersensitivity, leading to renewed interest in NMDA receptor antagonists such as ketamine [3].

Ketamine has been used as an anaesthetic–analgesic agent for more than 30 yr. Its mechanism of action has been disputed [4] but it is now generally agreed that one pharmacological mechanism of the antinociceptive action is specific binding to the phencyclidine (PCP) site of the NMDA receptor-gated ion channel. This results in non-competitive, use-dependent NMDA receptor antagonism [5]. In experimental studies ketamine reduced NMDA-mediated nociceptive responses in dorsal horn neurones [6]. Clinical studies with ketamine indicated a role for NMDA receptors in acute postoperative [7–10], and also chronic neuropathic pain [11, 12].

A cutaneous heat injury evokes hyperalgesia for mechanical and heat stimuli within the injured area (primary hyperalgesia) and hyperalgesia for mechanical, but not heat, stimuli in an area surrounding the injury (secondary hyperalgesia) [13]. There is convincing evidence that secondary hyperalgesia is a result of altered central processing of afferent input because of sensitization of dorsal horn neurones, whereas primary hyperalgesia seems to be caused by a combination of sensitization of peripheral receptors and central neurones [14–18]. The burn injury model has been used previously to study the effects of various analgesics in human volunteers [19, 20].

The aim of this study was to investigate the effects of systemic ketamine, in clinically relevant analgesic doses, on pain and hyperalgesia after a burn injury in human volunteers.

Subjects and methods

We studied 19 healthy, unmedicated male volunteers, aged 20–31 yr, after obtaining informed consent and approval from the regional Ethics Committee and the Danish National Health Board. The study was performed in a quiet room with the subjects in a semi-supine position. Each subject had been familiarized with the burn injury and measurement procedures on a separate day.

S. ILKJAER, MD, M. WERNBERG, MD, Department of Anaesthesiology, Skejby University Hospital, DK-8200 Skejby, Aarhus, Denmark. K. L. PETERSEN, MS, J. BRENNUM, MD (Department of Neurology), J. B. DAHL, MD, PHD (Department of Anaesthesiology); Glostrup University Hospital, DK-2600 Glostrup, Copenhagen, Denmark. Accepted for publication: January 12, 1996.

Correspondence to S.I.

HYPERALGESIA

Burn injuries were produced on the medial surface of the dominant calf (L3–4 dermatome), with a 25 × 50 mm rectangular thermode (Thermotest, Somedic A/B, Sweden), applied to the skin with a standardized pressure (8 kPa). The temperature of the thermode was 47 °C, and the application time was 7 min. This resulted in a first-degree burn injury, that is redness without blistering.

Pain ratings were performed continuously by the volunteer during the burn injury with an electronic visual analogue scale (VAS). The VAS was anchored with the descriptors "no pain" and "worst possible pain". Pain ratings were sampled at a rate of 2 Hz. The interpretation of "pain" was left to the subject, who was instructed to apply the same interpretation throughout the study.

Brief conditioning ("priming" of the central nervous system with afferent input in C-fibres) was produced with the same thermode placed on the centre of the anterior side of the thigh at 45 °C. After 3 min of heating, the border of hyperalgesia to punctuate stimuli was determined along four linear paths arranged radially around the thermal injury (see below). Immediately after these determinations the thermode was removed. These brief conditioning stimuli induced slight or no pain during heating and no spontaneous sensations after termination. The mechanical hyperalgesia induced by these brief conditioning stimuli never lasted more than a few minutes beyond the duration of the conditioning stimuli.

MEASUREMENT OF THERMAL THRESHOLDS

Thermal thresholds were measured with a computerized Thermotest (Somedic AB, Sweden). Heat pain detection threshold (HPDT) was defined as the lowest temperature perceived as painful. The thermode was identical to that used for production of the burn injury.

HPDT was determined from a baseline temperature of 32 °C with a rate of change of 1 °C s^{-1}. By pressing a button, subjects indicated when the pertinent threshold was reached. This value was recorded, and the stimulator returned to baseline. If the cut-off limit (52 °C) was reached before the pertinent threshold, the thermode automatically returned to baseline and a threshold of 52 °C was registered (this was the case in three of 570 threshold determinations). Each threshold was calculated as the average of three measurements with intervals of 10 s between each stimulation. Thermal thresholds were determined at the site of injury and at the corresponding site of the contralateral, unburned calf.

MEASUREMENT OF MECHANICAL HYPERALGESIA

The temperature of the injured site was stabilized at 36 °C, with the above described thermode, from 5 min before and throughout assessments of mechanical hyperalgesia. The border of hyperalgesia to punctuate and stroke stimuli was determined by stimulating along four linear paths arranged radially around the thermal injury in steps of 5 mm at intervals of 1 s, starting well outside the hyperalgesic area where neither stimulus type evoked pain. The stimulations continued towards the injury until subjects reported a clear change in sensation ("burning", "tenderness", "more intense pricking"). The areas of hyperalgesia were calculated using a vector algorithm [19]. Punctuate stimulation was performed with the von Frey technique using a nylon filament with a diameter of 1 mm and a bending force of 1.15 N. Stroke stimulation was performed by lightly stroking the skin with a gauze swab.

Table 1 Experimental design

Time	Actions/measurements
Baseline	Area of secondary hyperalgesia to pinprick during brief conditioning, thigh Heat pain detection threshold (HPDT), right and left calf
0–15 min	I.v. bolus of ketamine/placebo, followed by continuous i.v. infusion of ketamine/placebo
15–20 min	Side effects Area of secondary hyperalgesia to pinprick during brief conditioning, thigh HPDT, right and left calf
20–27 min	Burn injury, right calf; measurement of pain with electronic VAS during burn
60–80 min	Side effects Area of secondary hyperalgesia to pinprick during brief conditioning, thigh HPDT, right (burned) and left calf Secondary hyperalgesia to pinprick and stroke around burn injury, right calf
130–150 min	Side effects Area of secondary hyperalgesia to pinprick during brief conditioning, thigh HPDT, right (burned) and left calf Area of secondary hyperalgesia to pinprick and stroke around burn injury, right calf
150 min	Cessation of i.v. infusion with ketamine/placebo
200–220 min	Side effects Area of secondary hyperalgesia to pinprick during brief conditioning, thigh HPDT, right (burned) and left calf Area of hyperalgesia to pinprick and stroke around burn injury, right calf

ASSESSMENT OF SIDE EFFECTS

Drowsiness was assessed on an 11-point analogue scale (0 = completely awake; 10 = almost asleep). Discomfort was assessed on an 11-point analogue scale (0 = no discomfort; 10 = maximum discomfort). Hallucinations (yes/no) were registered after bolus injection. Finally, subjects were asked if they experienced other sensations (table 1).

EXPERIMENTAL PROCEDURE

On 3 separate days, at least 1 week apart, subjects received a bolus of either ketamine 0.15 mg kg^{-1}, ketamine 0.30 mg kg^{-1} or placebo, delivered by a mechanical infusion pump over 15 min. The bolus dose was followed by a continuous infusion of ketamine 0.15 mg kg^{-1} h^{-1}, ketamine 0.30 mg kg^{-1} h^{-1} or placebo, respectively, for 135 min. The time to administer the bolus injection and doses of ketamine were chosen on the basis of a small pilot study, performed in order to determine doses with acceptable side effects. The study was double-blind, and the order of treatments was randomized. The time course of the various assessments are shown in table 1.

STATISTICAL ANALYSIS

Data are presented as median (range). Variables were evaluated with non-parametric two-way analysis of variance for repeated measurements, Friedmann's analysis of variance and Wilcoxon's test for paired data, where appropriate. $P \leqslant 0.05$ was considered statistically significant.

Results

CONTROL (PLACEBO) DAY

Pain during burn injury increased rapidly during the first 15–30 s, reached a plateau and then remained relatively stable during the remaining 6 min (fig. 1). After injury, no spontaneous pain or other sensations were experienced from the site of injury.

HPDT inside the burn injury decreased from a baseline value of 45.9 (44.6–47.6) °C to 41.6 (39.0–44.8) °C, 100 min after the injury (Friedmann's ANOVA, $P < 0.00001$), and remained decreased throughout the study (fig. 2).

HPDT on the contralateral calf did not change during the study (fig. 2). The borders of secondary hyperalgesia for punctuate and stroke stimuli (fig. 3) surrounding the burn injury on the calf and the area of secondary hyperalgesia for punctuate stimuli evoked by brief conditioning on the thigh (fig. 4) were detected easily in all subjects.

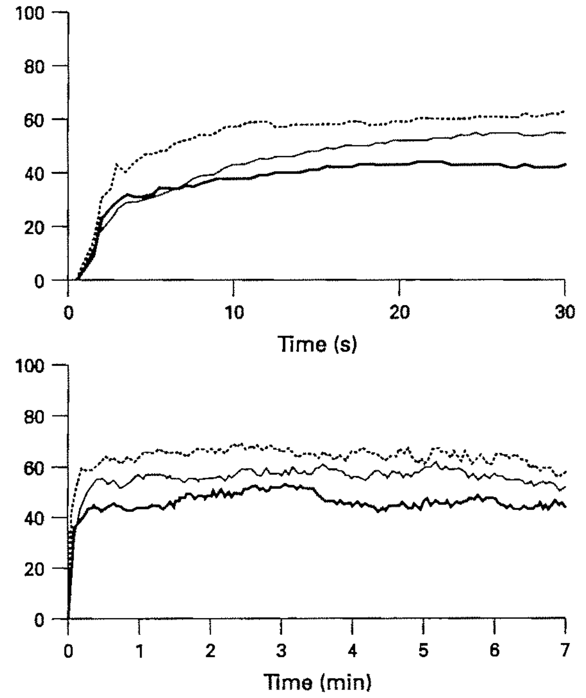


Figure 1 Pain (VAS) during burn injury during infusion of placebo (----), ketamine 0.15 mg kg^{-1} (——) or ketamine 0.30 mg kg^{-1} (——) (medians). The initial rapid increase in pain observed during placebo treatment (top) was diminished, and the plateau level was reduced (bottom) (ketamine 0.15 mg kg *vs* placebo: $P < 0.07$; ketamine 0.30 mg kg^{-1} *vs* placebo: $P < 0.007$, Wilcoxon rank test).

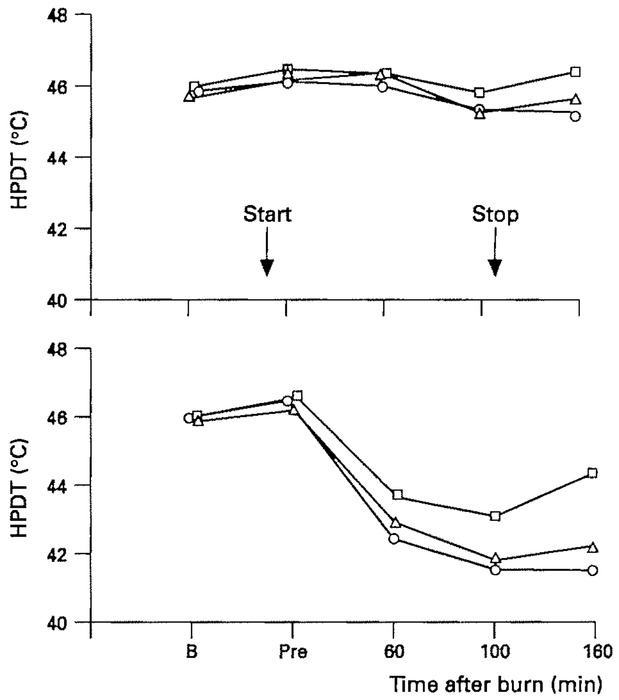


Figure 2 Heat pain detection threshold (HPDT) on the unburned (top) and burned (bottom) calf (medians) before (baseline (B) and before the burn injury (Pre)) during and after infusion of placebo (○), ketamine 0.15 mg kg^{-1} (△) or ketamine 0.30 mg kg^{-1} (□). Start, stop = Beginning and end of infusion of ketamine or placebo. Ketamine 0.15 mg kg^{-1} *vs* placebo: $P > 0.05$; ketamine 0.30 mg kg^{-1} *vs* placebo: $P > 0.05$, non-parametric two-way analysis for unburned calf; ketamine 0.15 mg kg^{-1} *vs* placebo: $P > 0.05$; ketamine 0.30 mg kg^{-1} *vs* placebo; $P < 0.05$, non-parametric two-way analysis for burned calf. Filled symbols = significant difference from baseline (Friedman's ANOVA).

EFFECTS OF KETAMINE

Pain during burn injury was reduced in a dose-dependent manner by ketamine (fig. 1). The initial rapid increase in pain observed during placebo treatment was diminished, and the plateau level was reduced (low-dose *vs* placebo, $P < 0.07$; high-dose *vs* placebo, $P < 0.007$; Wilcoxon rank test).

At the site of injury there was no difference in the decrease in HPDT between placebo and low-dose ketamine treatments ($P > 0.7$; two-way ANOVA), whereas HPDT was reduced less during high-dose ketamine compared with placebo after injury ($P < 0.03$; two-way ANOVA). Hence, high-dose ketamine diminished primary hyperalgesia (fig. 2).

At the contralateral uninjured calf there was no difference in HPDT either between low-dose ketamine and placebo or between high-dose ketamine and placebo ($P = 0.43$ and $P = 0.07$, respectively; two-way ANOVA) (fig. 2).

The areas of secondary hyperalgesia for punctuate and stroke stimuli were both reduced by high-dose ketamine compared with placebo ($P < 0.004$ and

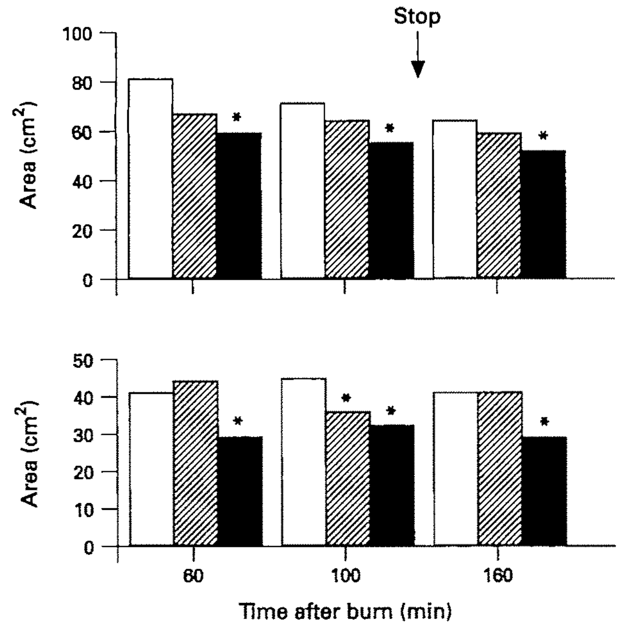


Figure 3 Top: Area of secondary hyperalgesia to punctuate stimuli around the burn injury during and after infusion of placebo (□), ketamine 0.15 mg kg^{-1} (▨) and ketamine 0.30 mg kg^{-1} (■) (medians). Ketamine 0.15 mg kg^{-1} *vs* placebo: $P > 0.05$; ketamine 0.30 mg kg^{-1} *vs* placebo: $P < 0.05$, non-parametric two-way analysis. $*P < 0.05$ compared with placebo. Bottom: Area of secondary hyperalgesia to stroke around the burn injury during and after infusion of placebo (□), ketamine 0.15 mg kg^{-1} (▨) and ketamine 0.30 mg kg^{-1} (■) (medians). Ketamine 0.15 mg kg^{-1} *vs* placebo: $P < 0.05$; ketamine 0.30 mg kg^{-1} *vs* placebo: $P < 0.05$, non-parametric two-way analysis. $*P < 0.05$ compared with placebo. Stop = End of infusion of ketamine or placebo.

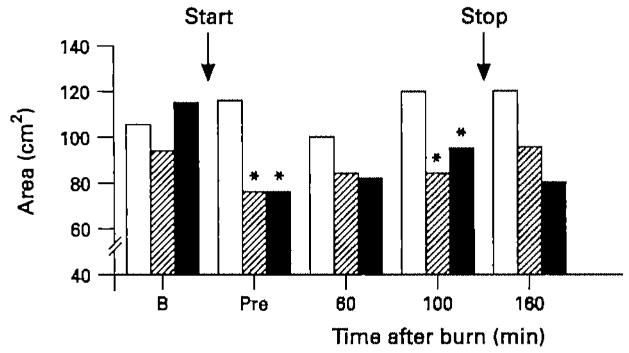


Figure 4 Area of secondary hyperalgesia to punctuate stimuli evoked by brief conditioning on the thigh before (baseline (B) and before the burn injury (Pre)), during and after infusion of placebo (□), ketamine 0.15 mg kg^{-1} (▨) and ketamine 0.30 mg kg^{-1} (■) (medians). Ketamine 0.15 mg kg^{-1} *vs* placebo: $P < 0.05$; ketamine 0.30 mg kg^{-1} *vs* placebo: $P < 0.05$, non-parametric two-way analysis. $*P < 0.05$, compared with placebo. Start, stop = Beginning and end of infusion of ketamine or placebo.

$P < 0.002$, respectively; two-way ANOVA) (fig. 3). Low-dose ketamine only reduced the area of secondary hyperalgesia for stroke ($P = 0.03$; two-way ANOVA) (fig. 3).

Both low- and high-dose ketamine reduced the area of secondary hyperalgesia for punctuate stimuli evoked by brief conditioning on the thigh ($P < 0.05$ and $P < 0.03$, respectively; two-way ANOVA) (fig. 4).

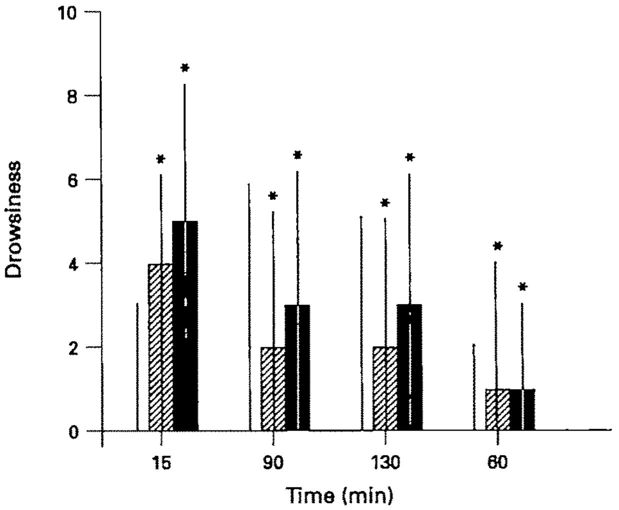


Figure 5 Drowsiness during and after infusion of placebo (□), ketamine 0.15 mg kg^{-1} (▨) and ketamine 0.30 mg kg^{-1} (■) (median, range) (15 = 15 min after ketamine bolus, 90 = 90 min after start of ketamine infusion, 130 = 130 min after start of ketamine infusion, 60 = 60 min after cessation of ketamine infusion). Ketamine 0.15 mg kg^{-1} *vs* placebo: $P < 0.05$; ketamine 0.30 mg kg^{-1} *vs* placebo: $P < 0.05$, non-parametric two-way analysis. $*P < 0.05$ compared with placebo.

SIDE EFFECTS

Ketamine induced drowsiness in all volunteers in a dose-dependent manner (fig. 5). Varying degrees of drowsiness (range 1–6 on the analogue scale), however, were also experienced by three volunteers during placebo treatment. Two volunteers experienced some degree of discomfort (range 1–6 on the analogue scale) after bolus injection of ketamine 0.15 mg kg^{-1} compared with five subjects after bolus injection of ketamine 0.30 mg kg^{-1} (range 2–9 on the analogue scale). No subject reported discomfort during continuous low-dose ketamine. Three subjects reported discomfort during continuous high-dose ketamine, although only one subject still experienced this discomfort towards the end of the infusion period. None of the volunteers experienced hallucinations. Most volunteers experienced other sensations such as "feeling drunk" or "dizzy" at one or several assessments during administration of ketamine. No volunteer wished to leave or was excluded from the study because of side effects. All volunteers were able to collaborate fully during the various assessments without problems.

Discussion

Experimental studies have demonstrated that dorsal horn neurones may display an altered response to both nociceptive and non-nociceptive afferent input after peripheral tissue damage or intense electrical C-fibre stimulation. These alterations include facilitation of the flexor motorneuronal responses, expansion of receptive fields and a decrease in the activation threshold of dorsal horn neurones [1,2]. The mechanisms of these alterations include induction of wind-up, whereby responses of dorsal horn neurones increase during repetitive constant intensity C-fibre stimuli, that is increased duration and magnitude of the cell responses [21]. There is substantial evidence that the NMDA receptor plays a significant role in wind-up and spinal hypersensitivity [1–3].

The mechanism of action of NMDA receptor antagonists differs from that of "classic" analgesics such as opioids. Opioids most probably reduce C-fibre input to the dorsal horn nociceptive neurones and consequently delay the onset and reduce the magnitude of wind-up and spinal hypersensitivity [22]. In contrast, the NMDA receptor antagonist ketamine has no effect on the initial input, but reduces wind-up [23]. Two recent studies in human volunteers confirmed these experimental observations [24, 25]. In one study, the NMDA receptor antagonist dextromethorphan reduced temporal summation of second pain, a psychophysical correlate of wind-up, whereas neither first nor second pain evoked by a single stimulus was affected by the drug [24]. In the other study, high-dose ketamine (bolus 0.5 mg kg^{-1}, followed by a 20-min infusion of 0.54 mg kg^{-1} h^{-1}) reduced central temporal summation to repeated nociceptive electrical stimuli, whereas reflex and pain ratings to a single stimulus were unaltered [25]. The high dose of ketamine used in the latter study [25], however, is clinically unacceptable because of significant side effects in the majority of patients [25].

Based on recent experimental and clinical studies, ketamine would be expected to have no or only minor effects on perception of non-noxious and phasic painful stimuli, such as thermal thresholds, in normal skin of human volunteers. Rather, ketamine is expected to exert its analgesic effects under conditions where tissue damage (e.g. a burn injury) or repetitive C-fibre stimulation has induced hyperexcitability of dorsal horn neurones. This study seems to confirm this assumption. Ketamine in clinically relevant, analgesic doses had no effect on thermal thresholds in undamaged skin, but reduced heat hyperalgesia at the site of injury. In contrast, HPDT in both normal and injured skin was increased after administration of extradural morphine 4 mg [20]. The differential effects of ketamine and morphine on thermal thresholds in normal and hyperalgesic skin are in agreement with the different mechanisms of action (see above).

Primary hyperalgesia is most probably caused by a combination of sensitization of peripheral receptors and central neurones, although the relative contribution of these components is not well established [13]. As ketamine increased HPDT in the primary hyperalgesic area, and as a peripheral effect of ketamine is not anticipated, the results of this study indicate that central sensitization contributes significantly to primary hyperalgesia. We observed further that pain during a prolonged noxious heat stimulus (which resulted in induction of secondary hyperalgesia and hence wind-up and sensitization of dorsal horn neurones), was reduced by ketamine in a dose-dependent manner. In accordance, Park and colleagues [26] reported reduction of ongoing pain evoked by intradermal capsaicin, and Arendt-Nielsen and colleagues [25] reduction of pain evoked by prolonged mechanical stimulation, by ketamine.

We observed that ketamine, in a dose-dependent manner, reduced secondary hyperalgesia for punctuate and stroke stimuli surrounding the burn injury, and secondary hyperalgesia for punctuate stimuli during brief thermal conditioning stimuli. In agreement with a previous study using higher doses of ketamine (bolus 5 mg, followed by infusion of 40 mg h^{-1}) [26], the reduction of the area of secondary hyperalgesia was only partial: 7–28% with low-dose ketamine and 25–28% with high-dose ketamine. Consequently, ketamine in clinically relevant doses should not by itself be expected to completely abolish pain or central sensitization [26, 27].

In experimental studies, NMDA receptor antagonists, including ketamine and dextromethorphan, have been shown to reduce tachyphylaxis and improve the analgesic effect of other analgesics such as morphine and local anaesthetics [28–32]. Data from clinical studies of postoperative pain are not uniform [7, 8]. In one study, the addition of ketamine 0.5 mg kg^{-1} to caudal bupivacaine provided better analgesia than bupivacaine alone in children undergoing inguinal herniotomy [7]. In another study, combined infusions of morphine and ketamine did not improve postoperative analgesia compared with morphine alone in patients undergoing elective upper abdominal surgery [8].

Side effects of the ketamine dose regimens used in this study were frequent but clinically acceptable in most volunteers. In general, side effects were most pronounced immediately after bolus injections, and substantially declined or disappeared during continuous infusions of both ketamine 0.15 and 0.30 mg kg^{-1} h^{-1}. Although ketamine in both doses produced drowsiness, HPDT in healthy skin was unaffected by ketamine. Consequently, we do not believe that drowsiness, or other side effects, introduced any significant bias.

In summary, ketamine reduced the magnitude of both primary and secondary hyperalgesia, and pain evoked by prolonged noxious heat stimulation. In contrast, ketamine did not alter phasic heat pain perception in undamaged skin. The analgesic effects of ketamine in the burn injury model can be distinguished from those of local anaesthetics and opioids [19, 20]. Side effects caused by continuous infusion of ketamine 0.15 mg kg^{-1} h^{-1} and 0.30 mg kg^{-1} h^{-1} were frequent but clinically acceptable in most human volunteers. These data provide a rationale for a systematic evaluation of the analgesic effect of low-dose ketamine in clinical pain states, such as postoperative pain.

Acknowledgement

This work was supported by a grant from the Sophus Johannsen Foundation.

References

1. Woolf CJ. Central mechanisms of acute pain. In: Bond MR, Charlton JE, Woolf CJ, eds. *Proceedings of the VIth World Congress on Pain.* Amsterdam: Elsevier, 1991; 25–34.
2. Woolf CJ. Somatic pain—pathogenesis and prevention. *British Journal of Anaesthesia* 1995; 75: 169–176.

3. Dickenson AH. NMDA receptor antagonists as analgesics. In: Fields HL, Liebeskind JC, eds. *Pharmacological Approaches to the Treatment of Chronic Pain: New Concepts and Critical Issues (Progress in Pain Research and Management, vol. 1)*. Seattle: IASP Press, 1994; 173–187.
4. Reich DL, Silvay G. Ketamine: an update of the first twenty-five years of clinical experience. *Canadian Journal of Anaesthesia* 1989; **36**: 186–197.
5. Lodge D, Johsson KM. Noncompetitive excitatory amino acid antagonists. *Trends in Pharmacological Science* 1990; **11**: 81–86.
6. Haley JE, Sullivan AF, Dickenson AH. Evidence for spinal *N*-methyl-D-aspartate receptor involvement in prolonged chemical nociception in the rat. *Brain Research* 1990; **518**: 218–226.
7. Naguib M, Sharif AMY, Seraj M, El Gammal M, Dawlatly AA. Ketamine for caudal analgesia in children: comparison with caudal bupivacaine. *British Journal of Anaesthesia* 1991; **67**: 559–564.
8. Edwards ND, Fletcher A, Cole JR, Peacock JE. Combined infusions of morphine and ketamine for postoperative pain in elderly patients. *Anaesthesia* 1993; **48**: 124–127.
9. Roytblat L, Korotkoruchko A, Katz J, Glazer M, Greemberg L, Fisher A. Postoperative pain: The effect of low-dose ketamine in addition to general anesthesia. *Anesthesia and Analgesia* 1993; **77**: 1161–1165.
10. Tverskoy M, Oz Y, Isakson A, Finger J, Bradley EL, Kissin I. Preemptive Effect of fentanyl and ketamine on postoperative pain and wound hyperalgesia. *Anesthesia and Analgesia* 1994; **78**: 205–209.
11. Eide PK, Jørum E, Stubhaug A, Bremnes J, Breivik H. Relief of post-herpetic neuralgia with the *N*-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. *Pain* 1994; **58**: 347–354.
12. Backonja M, Arndt G, Gombar KA, Check B, Zimmermann M. Response of chronic neuropathic pain syndromes to ketamine: a preliminary study. *Pain* 1994; **56**: 51–57.
13. Treede RD, Meyer RA, Raja SN, Campbell JN. Peripheral and central mechanisms of cutaneous hyperalgesia. *Progress in Neurobiology* 1992; **38**: 397–421.
14. Baumann TK, Simone DA, Shain CN, LaMotte RH. Neurogenic hyperalgesia: the search for the primary cutaneous afferent fibers that contribute to capsaicin-induced pain and hyperalgesia. *Journal of Neurophysiology* 1991; **66**: 212–227.
15. LaMotte RH, Lundberg LER, Torebjörk HE. Pain, hyperalgesia and activity in nociceptive C units in humans after intradermal injection of capsaicin. *Journal of Physiology (London)* 1992; **448**: 749–764.
16. LaMotte RH, Shain CN, Simone DA, Tsai EFP. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. *Journal of Neurophysiology* 1991; **66**: 190–211.
17. Simone DA, Sorkin LS, Oh O, Chung JM, Owens C, LaMotte RH, Willis WD. Neurogenic hyperalgesia: central neural correlates in responses of spinothalamic tract neurons. *Journal of Neurophysiology* 1991; **66**: 228–246.
18. Torebjörk E, Lundberg L, LaMotte R. Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. *Journal of Physiology (London)* 1992; **448**: 765–780.
19. Dahl JB, Brennum J, Arendt-Nielsen L, Jensen TS, Kehlet H. The effect of pre- versus postinjury infiltration with lidocaine on thermal and mechanical hyperalgesia after heat injury to the skin. *Pain* 1993; **53**: 43–51.
20. Brennum J, Dahl JB, Møiniche S, Arendt-Nielsen L. Quantitative sensory examination during epidural anaesthesia and analgesia in man. Effects of preemptive and posttraumatic morphine on hyperalgesia. *Pain* 1994; **59**: 261–271.
21. Dickenson AH, Sullivan AF. Evidence for a role of the NMDA receptor in the frequency dependent potentiation of the deep dorsal horn neurones following C-fibre stimulation. *Neuropharmacology* 1987; **26**: 1235–1238.
22. Dickenson AH, Sullivan AF. Electrophysiological studies on the effects of intrathecal morphine on nociceptive neurones in the rat dorsal horn. *Pain* 1986; **24**: 211–222.
23. Davies SN, Lodge D. Evidence for involvement of *N*-methyl-D-aspartate receptors in "wind-up" of class 2 neurones in the dorsal horn of the rat. *Brain Research* 1987; **424**: 402–406.
24. Price DD, Mao J, Frenk H, Mayer DJ. The *N*-methyl-D-aspartate receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man. *Pain* 1994; **59**: 165–174.
25. Arendt-Nielsen L, Petersen-Felix S, Fischer M, Bak P, Bjerring P, Zbinden AM. The effect of *N*-methyl-D-aspartate antagonist (ketamine) on single and repeated nociceptive stimuli: a placebo-controlled experimental human study. *Anesthesia and Analgesia* 1995; **81**: 63–68.
26. Park KM, Max MB, Robinovitz E, Gracely RH, Bennett GJ. Effects of intravenous ketamine and alfentanil on hyperalgesia induced by intradermal capsaicin. In: Gebhart DL, Hammond DL, Jensen TS, eds. *Proceedings of the 7th World Congress on Pain*. Seattle: IASP Press, 1994; 173–187.
27. Segerdahl M, Ekblom A, Sollevi A. The influence of adenosine, ketamine, and morphine on experimentally induced ischemic pain in healthy volunteers. *Anesthesia and Analgesia* 1994; **79**: 787–791.
28. Lee K-C, Wilder RT, Smith RL, Berde CB. Thermal hyperalgesia accelerates and MK-801 prevents the development of tachyphylaxis to rat sciatic nerve blockade. *Anesthesiology* 1994; **81**: 1284–1293.
29. Elliot K, Hynansky A, Inturrisi CE. Dextromethorphan attenuates and reverses analgesic tolerance to morphine. *Pain* 1994; **59**: 361–368.
30. Chapman V, Dickenson AH. The combination of NMDA antagonism and morphine produces profound antinociception in the rat dorsal horn. *Brain Research* 1992; **573**: 321–323.
31. Yamamoto T, Yaksh TL. Studies on the spinal interaction of morphine and the NMDA antagonist MK-801 on the hyperesthesia observed in a rat model of sciatic mononeuropathy. *Neuroscience Letters* 1992; **135**: 67–70.
32. Mao J, Price DD, Mayer DJ, Lu J, Hayes RL. Intrathecal MK-801 and local nerve anaesthesia synergistically reduce nociceptive behaviours in rats with experimental peripheral mononeuropathy. *Brain Research* 1992; **576**: 254–262.

British Journal of Anaesthesia 1996; **76**: 835–840

Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting

L. LÓPEZ-OLAONDO, F. CARRASCOSA, F. J. PUEYO, P. MONEDERO, N. BUSTO AND A. SÁEZ

Summary

We studied 100 ASA I–II females undergoing general anaesthesia for major gynaecological surgery, in a prospective, double-blind, placebo-controlled, randomized study. Patients received one of four regimens for the prevention of postoperative nausea and vomiting (PONV): ondansetron 4 mg ($n = 25$), dexamethasone 8 mg ($n = 25$), ondansetron with dexamethasone (4 mg and 8 mg, respectively, $n = 25$) or placebo (saline, $n = 25$) There were no differences in background factors or factors related to operation and anaesthesia, morphine consumption, pain or side effects between groups. The incidence of nausea and emetic episodes in the ondansetron with dexamethasone group was lower than in the placebo ($P < 0.01$), ondansetron ($P < 0.05$) and dexamethasone ($P = 0.057$) groups. There were no differences between ondansetron and dexamethasone, and both were more effective than placebo ($P < 0.05$ and $P < 0.01$, respectively). Dexamethasone appeared to be preferable in preventing nausea than emetic episodes. Fewer patients in the ondansetron with dexamethasone group needed antimetic rescue ($P < 0.01$ *vs* placebo and $P < 0.05$ *vs* ondansetron). We conclude that prophylactic administration of combined ondansetron and dexamethasone is effective in preventing PONV. (*Br. J. Anaesth.* 1996; **76**: 835–840).

Key words

Surgery, gynaecological. Vomiting, nausea. Vomiting, antimetics. Pharmacology, ondansetron. Pharmacology, dexamethasone.

Recent reviews have reported that the incidence of postoperative nausea and vomiting (PONV) is 30% [1, 2], with little improvement in recent years, but it may be higher because of the influence of preoperative patient characteristics, factors related to operation and anaesthesia, and the intensity of pain and its management in the postoperative period [3, 4].

The introduction into clinical practice of the 5-HT_3 receptor antagonist, ondansetron, has provided effective antiemesis in surgical patients without significant drug-related side effects [5, 6]. Dexamethasone has been used as an antiemetic for more than 10 yr in patients receiving chemotherapy, with limited side effects [7–11]. The mechanism of action of dexamethasone as an antiemetic is not known.

None of the available antiemetics is entirely effective in all patients, perhaps because there is no single stimulus for PONV. The combination of drugs currently used in the treatment of nausea and vomiting in patients receiving chemotherapy [8], could be a solution to control situations with severe, frequent PONV. Recently, the combination of ondansetron and dexamethasone has been shown to be a highly effective prophylactic measure for patients receiving high-dose cisplatin chemotherapy [8].

In this prospective, double-blind, randomized study, we assessed the safety and efficacy of a single i.v. dose of ondansetron 4 mg, dexamethasone 8 mg, ondansetron with dexamethasone (4 mg and 8 mg, respectively) or placebo (2 ml of saline) in females undergoing elective major gynaecological surgery.

Patients and methods

After obtaining local Ethics Committee approval and written informed consent, we studied 100 ASA I – II women, aged 18–65 yr, weighing 45–90 kg, undergoing major elective gynaecological surgery. Patients who had received opioids, NSAID, steroids or antiemetic agents during the previous month or who had hypersensitivity to either ondansetron or steroids were excluded.

Patients were allocated randomly to one of four groups: P (placebo), O (ondansetron), D (dexamethasone) and O+D (ondansetron with dexamethasone). The study was prospective, conducted in a double-blind manner, with a stratified randomization to ensure an equal number of patients of the same age and weight undergoing the same type of surgery in each group (Table 1).

The night before surgery we recorded the following variables: age, weight and height, previous general anaesthesia and abdominal surgery, history

---

L. LÓPEZ-OLAONDO*, MD, PHD, F. CARRASCOSA, MD, PHD, F. J. PUEYO, MD, PHD, P. MONEDERO, MD, PHD, N. BUSTO, MD, PHD, A. SÁEZ, MD, PHD, Department of Anaesthesiology and Critical Care, University Clinic, School of Medicine, University of Navarra, Pamplona, Spain. Accepted for publication: February 7, 1996.

*Address for correspondence: Departamento de Anestesiología, Clínica Universitaria, Apartado 192, 31080 Pamplona, Spain.

Table 1 Patient data (number of patients)

	Group			
	P	O	D	O and D
n	25	25	25	25
Age (yr)				
< 40	5	5	5	5
40—60	17	17	17	17
> 60	3	3	3	3
Weight (kg)				
< 60	9	9	9	10
60–80	15	16	15	14
> 80	1	0	1	1
Type of surgery				
Hysterectomy	20	20	20	20
Adnexectomy	2	2	2	2
Second look laparotomy	2	2	2	2
Myomectomy	1	1	1	1

of motion sickness or headache, history of PONV after previous surgery, phase of menstrual cycle and grade of anxiety. All patients were taught to use the patient-controlled analgesia (PCA) pump for self-administration of morphine and were told to call the nurse as soon as they felt nausea or had any emetic episode in the postoperative period.

All patients had their last oral intake at least 8 h before the start of anaesthesia and were premedicated with bromazepam 0.1 mg kg^{-1} administered orally the night before surgery and atropine 0.01 mg kg^{-1} i.m., 30 min before induction of anaesthesia.

Each patient received two syringes with 2 ml of solution before induction of anaesthesia. Patients in group P received 0.9% saline, those in group O, ondansetron 4 mg and 0.9% saline, those in group D, dexamethasone 8 mg and 0.9% saline, and those in group O and D, ondansetron 4 mg and dexamethasone 8 mg.

Anaesthesia was induced with thiopentone 5 mg kg^{-1}, atracurium 0.5 mg kg^{-1} and fentanyl 5μg kg^{-1}. The trachea was intubated 3 min after administration of atracurium. A nasogastric tube and a urinary catheter were placed in all patients. Anaesthesia was maintained with 50% nitrous oxide in oxygen supplemented with isoflurane (0.5–1% expired concentration). Ventilation was adjusted to maintain end-tidal carbon dioxide pressure at 4.7 kPa. Neuromuscular blocking agents and fentanyl were used as required. All patients received morphine 0.1 mg kg^{-1} when it was predicted that surgery would end in 30 min. It was not necessary to antagonize residual neuromuscular block in any patient. No other sedative, analgesic or antiemetic drug was administered. The nasogastric tube and urinary catheter were left in place.

The variables recorded during the operative period included: type of incision (Pfannenstiel or midline laparotomy), type of surgery (hysterectomy, adnexectomy, reassessment laparotomy (second look) for ovarian cancer or myomectomy), total amount of atracurium and fentanyl administered, and duration of surgery and anaesthesia.

Postoperative analgesia was provided with i.v. ketorolac 30 mg/8 h and PCA (Pain Management Provider TM, Abbott, North Chicago, IL, USA) morphine 1 mg ml^{-1} (demand dose = 1 mg; lockout interval = 10 min; and maximum dose in 4 h = 0.25 mg kg^{-1}).

In the recovery room (2 h) and in the ward (12, 24 and 48 h after recovery from anaesthesia) we studied the following variables: in (1) incidence of PONV—we asked patients if they felt nauseated or sick in each period, with only two possible answers, "yes" if they did for at least 10 min, or "no". Retching and vomiting were grouped together under the common term "emetic episode" and were assessed as present or absent. The primary end-point was a complete response, as defined by no nausea or emetic episodes during the 48-h postoperative period. (2) Number of patients who needed rescue antiemetic treatment—if patients experienced nausea for 30 min or more than one emetic episode in 15 min, rescue antiemetic treatment was available with metoclopramide 10 mg/8 h. (3) Pain intensity scores, with and without active movement, were obtained with the VAS test. They were classified into three categories to allow easier statistical analysis. The pain categories were: severe if VAS score was greater than 7, moderate if VAS score was 3–7 and light if VAS score was less than 3. (4) Total amount of morphine consumed. (5) Sedation five-point scale: 4 = completely awake, open eyes; 3 = drowsy, closed eyes; 2 = asleep, responds to oral call; 1 = asleep, responds to touch or pain; 0 = does not respond). (6) Other side effects.

All observations were made by the same previously trained nurses as soon as the symptoms appeared. Nausea, retching and vomiting were also assessed by the same anaesthetist by questioning the patient 2, 12, 24 and 48 h after recovery from anaesthesia. Both the nurses and the anaesthetist were unaware of which antiemetic the patient had received.

We also recorded the following variables: postoperative comfort, postoperative analgesia and night rest (rated as bad, fair, good and very good), postoperative comfort compared with previous experiences (rated as worse, similar, better and not comparable), time before first postoperative oral intake, time before standing up and moment at which nasogastric tube and urinary catheter were removed (rated as less than 12 h, at 12–24 h, at 24–36 h, at 36–48 h and more than 48 h).

We used the chi-square test and Fisher's exact test for non-parametric analysis. Parametric data were analysed using analysis of variance (Fisher's PLSD correction was also applied), Kruskal–Wallis and Mann–Whitney tests. $P < 0.05$ was considered significant.

Results

The incidence of background factors and factors related to operation and anaesthesia, which may modify PONV, did not differ between groups (table 2).

A complete response (no nausea and no emetic episodes during the 48-h postoperative period) occurred in 84% of patients in the ondansetron with dexamethasone group and in only 20% of patients in the placebo group ($P < 0.01$). In the ondansetron

Table 2 Background factors and those related to operation and anaesthesia (mean (SD or range) or number of patients)

	Group			
	P	O	D	O and D
n	25	25	25	25
Age (yr)	47 (22–65)	47 (21–63)	46 (26–65)	46 (19–65)
Weight (kg)	63 (8)	62 (10)	62 (8)	64 (8)
Height (cm)	160 (5)	159 (6)	160 (5)	160 (5)
Motion sickness (*n*)	4	8	7	6
Headache (*n*)	2	2	3	4
Anxiety (*n*)				
Calm	7	3	4	6
Nervous	9	15	16	15
Very nervous	9	7	5	4
Menstrual cycle (*n*)				
Days 1–6	4	5	3	7
Days 7–16	5	5	4	4
Days 17–(−1)	4	5	3	5
Postmen.–Amenorr.	12	10	15	9
Previous general anaesthesia	10	12	11	16
Previous abdominal surgery	6	11	9	8
History of PONV	3	4	4	6
Type of incision				
Pfannenstiel	20	15	19	20
Midline laparotomy	5	10	6	5
Atracurium (mg kg^{-1})	0.7 (0.1)	0.7 (0.1)	0.7 (0.2)	0.8 (0.2)
Fentanyl (μg kg^{-1})	5.9 (0.9)	6.0 (1.2)	5.7 (0.8)	5.6 (0.6)
Duration of surgery (min)	109 (24)	116 (31)	111 (46)	117 (30)
Duration of anaesthesia (min)	132 (25)	137 (33)	137 (47)	136 (30)

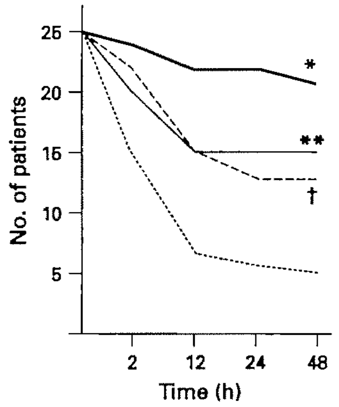


Figure 1 Number of patients without PONV from the end of surgery until the moment of each evaluation. Number and percentage of patients with a complete response: group O+D (——) ($n = 21$, 84%); group D (——) ($n = 15$, 60%); group O (-—) ($n = 13$, 52%) and group P (.....) ($n = 5$, 20%). *$P <$ 0.05 *vs* group O and $P < 0.01$ *vs* group P; **$P < 0.01$ *vs* group P; †$P < 0.05$ *vs* group P.

Table 3 Number of patients (%) with nausea and emetic episodes (EE) from the end of surgery until the moment of each evaluation. Significant difference ($P < 0.05$) compared with: *group P; †group O; ‡group D

	Group			
	P	O	D	O and D
n	25	25	25	25
2 h				
Nausea	10 (40)	3 (12)*	5 (20)	1 (4)*
EE	6 (24)	0 (0)*	3 (12)	0 (0)*
12 h				
Nausea	18 (72)	10 (40)*	10 (40)*	3 (12)*†‡
EE	11 (44)	3 (12)*	8 (32)	1 (4)*‡
24 h				
Nausea	19 (76)	12 (48)*	10 (40)*	3 (12)*†‡
EE	11 (44)	6 (24)	8 (32)	1 (4)*†‡
48 h				
Nausea	20 (80)	12 (48)*	10 (40)*	4 (16)*†
EE	12 (48)	6 (24)	8 (32)	1 (4)*†‡

group, it occurred in 52% of patients and in 60% of patients in the dexamethasone group (fig. 1).

The incidence of nausea and emetic episodes in patients in group O+D was lower than in those in groups P, O and D during the whole study. There were significant differences between groups O+D and P at all times ($P < 0.01$), and between group O+D and groups O and D at some times only (table 3). There were no differences in the frequencies of nausea and emetic episodes between patients who received ondansetron or dexamethasone.

Only two patients (8%) in group O+D required antiemetic rescue ($P < 0.01$ *vs* group P and $P <$ 0.05 *vs* group O), compared with seven patients (28%) in group D ($P < 0.01$ *vs* group P), nine patients (36%) in group O ($P < 0.05$ *vs* group P) and 17 patients (68%) in group P.

There were no significant differences in pain intensity between groups at any time. At the end of the study only two patients at rest and 21 with movement had a VAS score greater than 3 (table 4).

Opioid requirements did not differ between groups, although in groups D and O+D, requirements were greater from 12 h after the end of operation. Mean total consumption of morphine at 48 h from the end of surgery was 32 (SD 14.8), (range 5–63) mg in group P, 32 (18.7), (4–68) mg in group O, 39 (22.4), (8–79) mg in group D and 38 (24.6), (4–94) mg in group O+D.

There were no significant differences in sedation. There was no patient with category 0, 1 or 2 at any

Table 4 Number of patients (%) in the different pain categories in each treatment group and period. The pain categories were: light (VAS 0 < 3), moderate VAS 3–7) and severe (VAS > 7–10)

	Group			
	P ($n = 25$)	O ($n = 25$)	D ($n = 25$)	O and D ($n = 25$)
2 h				
Light	16 (64)	11 (44)	13 (52)	16 (64)
Moderate	9 (36)	13 (52)	12 (48)	9 (36)
Severe	—	1 (4)	—	—
12 h rest				
Light	18 (72)	19 (76)	14 (56)	13 (52)
Moderate	7 (28)	6 (24)	11 (44)	12 (48)
Severe	—	—	—	—
12 h mov.				
Light	5 (20)	2 (8)	6 (24)	4 (16)
Moderate	16 (64)	19 (76)	13 (52)	14 (56)
Severe	4 (16)	4 (16)	6 (24)	7 (28)
24 h rest				
Light	23 (92)	25 (100)	22 (88)	23 (92)
Moderate	2 (8)	—	3 (12)	2 (8)
Severe	—	—	—	—
24 h mov.				
Light	11 (44)	16 (64)	10 (40)	9 (36)
Moderate	13 (52)	9 (36)	12 (48)	14 (56)
Severe	1 (4)	—	3 (12)	2 (8)
48 h rest				
Light	24 (96)	25 (100)	25 (100)	24 (96)
Moderate	1 (4)	—	—	1 (4)
Severe	—	—	—	—
48 h mov.				
Light	22 (88)	21 (84)	19 (76)	17 (68)
Moderate	3 (12)	4 (16)	6 (24)	8 (32)
Severe	—	—	—	—

time during the study. At 12 h after the end of surgery, there were only seven patients with category 3, and all patients were in category 4 by 24 h (table 5).

The percentage of adverse events was similar between groups (table 4). The most commonly reported adverse event was headache. Perineal itching was reported during administration of a solution in groups that received dexamethasone, but disappeared spontaneously in 30 s. Itching was the only adverse effect associated with a high consumption of morphine.

No patient scored postoperative comfort as bad. Comfort was found to be greater in group O+D than group P at 24 h ($P < 0.05$) (Fig. 2). There were no differences between groups at 48 h and only 11 % of patients defined postoperative comfort as fair, most because of PONV.

Night rest was similar between groups. No patient considered night rest as bad. Four patients in group P, one patient in group O, one in group D and two in group O+D defined the first night's rest as fair mainly because of PONV. Fourteen patients (five patients in group P, three patients in group O, two in group D and four in group O+D) described rest as fair on their second night mainly because of lack of their usual hypnotics at home (10 patients) and PONV.

Postoperative comfort was similar to previous surgical experiences in 8 % of patients, not comparable in 20 % and better in 72 %. There were no significant differences between groups.

Table 5 Number of patients with different categories of sedation in each group and period (categories of sedation: 4 = completely awake, open eyes; 3 = drowsy, closed eyes; 2 = asleep, answer to oral call; 1 = asleep, answer to touch or pain; 0 = does not respond)

	Group			
	P ($n = 25$)	O ($n = 25$)	D ($n = 25$)	O and D ($n = 25$)
2 h				
4	14 (56)	16 (64)	18 (72)	13 (52)
3	11 (44)	9 (36)	7 (28)	12 (48)
2	—	—	—	—
1	—	—	—	—
0	—	—	—	—
12 h				
4	22 (88)	24 (96)	22 (88)	25 (100)
3	3 (12)	1 (4)	3 (12)	—
2	—	—	—	—
1	—	—	—	—
0	—	—	—	—
24 h				
4	25 (100)	25 (100)	25 (100)	25 (100)
3	—	—	—	—
2	—	—	—	—
1	—	—	—	—
0	—	—	—	—
48 h				
4	25 (100)	25 (100)	25 (100)	25 (100)
3	—	—	—	—
2	—	—	—	—
1	—	—	—	—
0	—	—	—	—

Table 6 Adverse events. Number of patients in each treatment group

	Group			
	P	O	D	O and D
n	25	25	25	25
Headache	2	3	1	3
$Sp_{O_2} < 94\%$ after 2 h in recovery room with $FI_{O_2} = 0.21$	2	1	1	2
Perineal itching	—	—	3	2
Abdominal distension	1	—	2	1
Urinary retention	—	2	1	—
Itching	1	—	1	—

There were no differences between groups in time before removal of the urinary catheter and nasogastric tube, time before standing up and time before oral intake.

Discussion

We found that during the 48 h period after recovery from anaesthesia, ondansetron 4 mg and dexamethasone 8 mg were more effective than placebo in preventing nausea, although there were no significant differences in vomiting, perhaps because the groups were small. Moreover, there were no significant differences between dexamethasone and ondansetron and both drugs offered adequate control of PONV. But the major finding was that in the 48-h period, the combination of ondansetron and dexamethasone was more effective than placebo and ondansetron alone for nausea and vomiting, and better than dexamethasone for vomiting but not for nausea. No

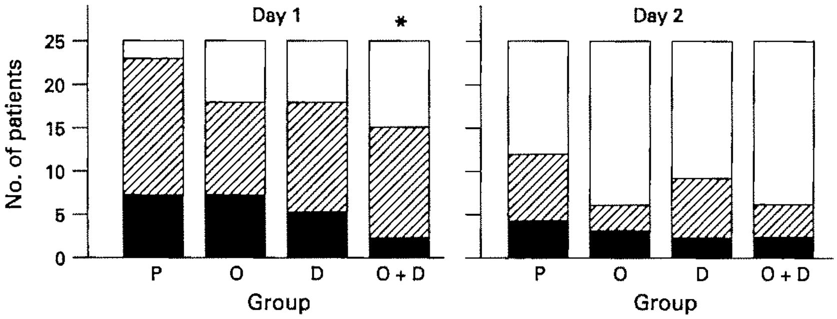


Figure 2 Grade of comfort after surgery. Number of patients who felt bad (none), fair (■), good (▨) or very good (□) in each treatment group. *$P < 0.05$ *vs* group P.

patient had vomiting in the recovery room (first 2 h) in the ondansetron with dexamethasone group, and only one patient during the 48-h postoperative period. Moreover, there was only one patient with nausea in the recovery room and only four had nausea during the 48-h postoperative period.

We chose patients at high risk of PONV: women aged 18–65 yr, in whom the incidence of PONV is three times higher [1, 2], undergoing major gynaecological surgery, a type of surgery associated with the highest incidence of PONV [2–4, 12]. We analysed factors that have been shown to affect the incidence of PONV such as patient weight [1, 2], history of motion sickness [3] or PONV after previous anaesthesia [12], grade of anxiety [1, 2] and phase of menstrual cycle [13]. In our study all of these factors were well balanced between groups. All patients underwent the same preoperative fasting and premedication, the same standardized balanced anaesthesia, without antagonism of neuromuscular block, and the same postoperative care, including the techniques and drugs used for postoperative analgesia. Type of incision, total amount of atracurium and fentanyl administered and duration of operation (none for more than 4 h) were similar in all groups. All of these factors also increase the incidence of PONV [1–4]. Postoperative factors involved in PONV [1–4], such as intensity of postoperative pain, morphine consumption, time to oral intake, time to stand up and time to remove nasogastric tube, were matched equally between groups.

Ondansetron is a selective 5-HT_3 receptor antagonist, effective in preventing PONV [6, 12, 13, 14–17]. The effectiveness of i.v. ondansetron as a prophylactic postoperative antiemetic was evaluated by McKenzie and colleagues in a dose ranging study [15], and it was demonstrated that a single 4-mg i.v. dose appeared to be the lowest acceptable dose to prevent PONV. Since then, most authors have agreed that this i.v. dose before induction is effective antiemetic prophylaxis [6, 18].

Dexamethasone was first reported to be an effective antiemetic agent in patients undergoing cancer chemotherapy in 1981 [7]. Since then randomized, placebo-controlled studies have shown that dexamethasone and other steroids are significantly better than other agents (metoclopramide, prochlorperazine, droperidol, domperidone) in preventing nausea and vomiting associated with chemotherapy. The mechanism of dexamethasone-induced antiemetic activity is not fully understood, but may involve central inhibition of prostaglandin synthesis [19]. Another theory involves a decrease in 5-HT turnover in the central nervous system [20] or changes in the permeability of the blood CSF barrier to serum proteins [21]. However, there is no experimental proof to support these hypotheses. The plasma elimination half-life of dexamethasone is approximately 4–4.5 h, similar to that of other antiemetics usually administered in a single dose [22] (for instance, ondansetron has a plasma half-life of approximately 3 h) [23]. A dose ranging study by Drapkin and Sokl [9] evaluated the effectiveness of i.v. dexamethasone in patients undergoing chemotherapy. An 8-mg i.v. dose appeared to be as effective as 32 mg in preventing nausea and vomiting in cancer chemotherapy. These are reasons why we chose dexamethasone as an antiemetic in a single 8-mg dose. A retrospective study by Mataruski and colleagues [24] showed that 34 patients who received intraoperative steroids were less likely to experience PONV than 27 who did not. Recently, Yoshitaka, Hiroyoshi and Hidenori [25] found no differences between placebo, granisetron and dexamethasone in women undergoing general anaesthesia for major gynaecological surgery. The lack of differences between the groups could be because of the low incidence of PONV and the small number of patients in the study.

McKenzie and colleagues [26] studied ondansetron and ondansetron with dexamethasone in women undergoing major gynaecological surgery and the results showed that the combination was more effective than ondansetron alone, as our results confirmed. More recently, Yoshitaka, Hiroyoshi and Hidenori [25] found differences between granisetron with dexamethasone and placebo, granisetron and dexamethasone alone, in women undergoing general anaesthesia for major gynaecological surgery.

All groups had a similar percentage of patients reporting adverse events. Perineal itching was present only in groups who received dexamethasone, and it appears to be related to the vehicle [11]. Chronic treatment with large doses of steroids has been implicated in postoperative complications such as infection and delayed or poor wound healing [27]. Many complications are dose related, and with low dose or discontinuation of steroids, their frequency decreases rapidly [28]. Furthermore, we did not find that giving a single large dose of steroid interfered with wound healing after surgery or produced other major side effects.

There were no significant differences between groups in sedation. The small number of patients with grade 3 sedation at 12 h had a higher consumption of morphine.

Pain and PONV are the most common, unpleasant postoperative events. As pain was similar in all groups, the lower incidence of PONV in our study was the main reason for the better results in group O+D compared with group P at 24 h. Both ondansetron and dexamethasone provided adequate control of PONV. If our results are confirmed in larger studies, dexamethasone will be more advantageous than ondansetron in terms of cost and resource allocation. The combination of ondansetron with dexamethasone was the most effective in reducing PONV. This combination could be useful in day-case surgical procedures because of the absence of side effects and sedation.

References

1. Watcha MF, White PF. Postoperative nausea and vomiting: its etiology, treatment and prevention. *Anesthesiology* 1992; **77**: 162–184.
2. Lerman J. Surgical and patient factors involved in postoperative nausea and vomiting. *British Journal of Anaesthesia* 1992; **69** (Suppl. 1): 24S–32S.
3. Korttila K. The study of postoperative nausea and vomiting. *British Journal of Anaesthesia* 1992; **69** (Suppl. 1): 20S–23S.
4. Haigh CG, Kaplan LA, Durham JM, Dupeyron JP, Harmer M, Kenny GN. Nausea and vomiting after gynaecological surgery: a meta-analysis of factors affecting their incidence. *British Journal of Anaesthesia* 1993; **71**: 517–522.
5. Scuderi P, Wetchler B, Sung Y-F, Mingus M, DuPen S, Claybon L, Leslie J, Talke P, Apfelbaum J, Sharif-Azad S. Treatment of postoperative nausea and vomiting after outpatient surgery with the 5-HT$_3$ antagonist ondansetron. *Anesthesiology* 1993; **78**: 15–20.
6. Pearman MH. Single dose intravenous ondansetron in the prevention of postoperative nausea and vomiting. *Anaesthesia* 1994; **49** (Suppl.): 11–15.
7. Aapro MS, Alberts DS. Dexamethasone as an antiemetic in patients treated with cisplatin. *New England Journal of Medicine* 1981; **305**: 520.
8. Smith DB, Newlands ES, Rustin GJ, Begent RH, Howells N, McQuade B, Bagshawe KB. Comparison of ondansetron and ondansetron plus dexamethasone as antiemetic prophylaxis during cisplatin containing chemotherapy. *Lancet* 1991; **338**: 487–490.
9. Drapkin RL, Sokl GH. The antiemetic effect and dose response of dexamethasone in patients receiving cis-platinum *Proceedings of the American Society of Clinical Oncology* 1982; **1**: 64.
10. Jones AL, Hill AS, Soukop M, Hutcheon AW, Cassidy J, Kaye SB, Sikora K, Carney DN, Cunningham D. Comparison of dexamethasone and ondansetron in the prophylaxis of emesis induced by moderately emetogenic chemotherapy. *Lancet* 1991; **338**: 483–486.
11. Allan SG, Leonard RCF. Dexamethasone antiemesis and side-effects. *Lancet* 1986; **1** 1035.
12. Kenny GNC. Risk factors for postoperative nausea and vomiting. *Anaesthesia* 1994; **49** (Suppl.): 6–10.
13. Helmers JH, Briggs L, Abrahamsson J, Soni J, Moodley J, Forrler M, Hellstein K. A single iv dose of ondansetron 8 mg prior to induction of anaesthesia reduces postoperative nausea and vomiting in gynaecological patients. *Canadian Journal of Anaesthesia* 1993; **40**: 1155–1161.
14. Rust M, Cohen LA. Single oral dose ondansetron in the prevention of postoperative nausea and emesis. *Anaesthesia* 1994; **49** (Suppl.): 16–23.
15. McKenzie R, Kovac A, O'Connor T, Duncalf D, Angel J, Gratz I, Tolpin E, McLeskey C, Joslyn A. Comparison of ondansetron versus placebo to prevent postoperative nausea and vomiting in women undergoing ambulatory gynecologic surgery. *Anesthesiology* 1993; **78**: 21–28.
16. Leeser J, Lip H. Prevention of postoperative nausea and vomiting using ondansetron, a new selective 5-HT$_3$ receptor antagonist. *Anesthesia and Analgesia* 1991; **72**: 751–755.
17. Kenny GNC, Oates JD, Leeser J, Rowbotham DJ, Lip H, Rust M, Saur P, Onsrud M, Haigh CG. Efficacy of orally administered ondansetron in the prevention of postoperative nausea and vomiting: a dose ranging study. *British Journal of Anaesthesia* 1992; **68**: 466–470.
18. Joslyn AF. Ondansetron, clinical development for postoperative nausea and vomiting: current studies and future directions. *Anaesthesia* 1994; **49** (Suppl.): 34–37.
19. Aapro MS, Plezia PM, Alberts DS, Graham V, Jones SE, Suwit EA, Moun TE. Double-blind cross-over study of the antiemetic efficacy of high-dose dexamethasone versus high-dose metoclopramide. *Journal of Clinical Oncology* 1984; **2**: 466–471.
20. Fredrikson M, Hursti T, Furst CJ, Steineck G, Borjeson S, Wikblom M, Peterson C. Nausea in cancer chemotherapy is inversely related to urinary cortisol excretion. *British Journal of Cancer* 1992; **65**: 779–780.
21. Livera P, Trojano M, Simone IL. Acute changes in blood CSF barrier permselectivity to serum protein after intrathecal methotrexate and CNS irradiation. *Journal of Neurology* 1985, **231**: 336–339.
22. Brady ME, Sartiano GP, Rosenblum JL, Zaglema NE, Bauguess CT. The pharmacokinetics of single high dose of dexamethasone in cancer patients. *European Journal of Clinical Pharmacology* 1987; **32**: 593–596.
23. Russell D, Kenny GNC. 5-HT$_3$ antagonists in postoperative nausea and vomiting. *British Journal of Anaesthesia* 1992; **69** (Suppl. 1): 63S–68S.
24. Mataruski MR, Keis NA, Smouse DJ, Workman ML. Effects of steroids on postoperative nausea and vomiting. *Nurse Anesthesia* 1990; **1**: 183–188.
25. Yoshitaka F, Hiroyoshi T, Hidenori T. Granisetron–dexamethasone combination reduces postoperative nausea and vomiting. *Canadian Journal of Anaesthesia* 1995; **42**: 387–390.
26. McKenzie R, Tantisira B, Karambelkar DJ, Riley TJ, Abdelhady H. Comparison of ondansetron with ondansetron plus dexamethasone in the prevention of postoperative nausea and vomiting. *Anesthesia and Analgesia* 1994; **79**: 961–964.
27. Uthoff K, Zehr KJ, Gaudin PB, Kumar P, Cho PW, Vogelsang G, Hruban RH, Baungartner WA, Stuart RS. Thalidomide as replacement for steroids in immunosupression after lung transplantation. *Annals of Thoracic Surgery* 1995 **59**: 277–282.
28. Min DI, Monaco AP. Complications associated with immunosuppressive therapy and their management. *Pharmacotherapy* 1991; **11**: 119S–125S.

British Journal of Anaesthesia 1996; **76**: 841–846

LABORATORY INVESTIGATIONS

Differential effects of desflurane and halothane on peripheral airway smooth muscle

A. J. MAZZEO, E. Y. CHENG, Z. J. BOSNJAK, R. L. COON AND J. P. KAMPINE

Summary

Volatile anaesthetics have been shown to have direct relaxant effects on airway smooth muscle. We have examined the effects of 0.9, 1.9, and 2.8 dog MAC of desflurane and halothane on isolated proximal and distal canine airways precontracted with acetylcholine. The proximal and distal airway smooth muscle relaxed with increasing concentration of each anaesthetic in a dose-related manner. Desflurane had a greater relaxant effect than halothane on the proximal airway only at 2.8 MAC. Desflurane relaxed the distal airway to a greater extent than halothane at 1.9 and 2.8 MAC. The distal airway smooth muscle was more sensitive to volatile anaesthetics than the proximal airway smooth muscle with either halothane or desflurane at all concentrations tested. This effect may be a result of differences in cartilage content, myosin content, epithelium-dependent effects, receptor density, myofilament sensitivity to Ca^{2+}, sarcoplasmic reticulum Ca^{2+} control, or ionic fluxes in the proximal airway compared with the distal airway. The increased sensitivity of airway smooth muscle to desflurane compared with halothane is not known but may be related to possible differences in the effects of Ca^{2+} homeostasis. (*Br. J. Anaesth.* 1996; **76**: 841–846)

Key words

Anaesthetics volatile, halothane. Anaesthetics volatile, desflurane. Airway, muscles. Receptors, cholinergic. Dog.

The bronchodilator effects of desflurane on intraparenchymal airway have not yet been determined. Adverse effects such as coughing and laryngospasm on induction have been associated with desflurane [1]. Although these effects appear to occur in the upper airway, it is not known if they are associated with a detrimental bronchospastic effect distally.

In this study we examined the direct effects of desflurane and halothane on the third- and sixth-generation airway. These segments of the peripheral airway are likely to be main sites of airway resistance [2] and airflow regulation [3, 4]. The clinical importance of direct effects of volatile anaesthetics on peripheral airway smooth muscle is not known. However, the direct effects on peripheral airway smooth muscle may be relevant clinically because of the diminishing innervation of airway smooth muscle when proceeding along the bronchial tree distally [5]. In addition, the airway at this level of the bronchial tree is more sensitive and more reactive [3, 6, 7], and therefore the distal airway requires less circulating agonist for a given response than proximally located airway. These factors may allow better control at the peripheral site of airflow regulation through a hormonal component rather than a neural component. This site of airflow regulation may therefore be affected predominately by the direct effects of anaesthetics, thereby altering airflow distribution. In this study we have determined the effects of halothane and desflurane on the portion of the airway believed to have a significant role in airflow regulation.

Materials and methods

All experimental procedures were approved by the Animal Care Committee of the Medical College of Wisconsin.

TISSUE PREPARATION

The right upper lobe was obtained from 15 mongrel dogs of both sexes (10–15 kg) after halothane anaesthesia and exsanguination. The right upper lobe, chosen to maintain consistency and ease of dissection [8], was placed in ice-cooled Krebs–Ringer bicarbonated solution aerated with 95% oxygen and 5% carbon dioxide. The first intraparenchymal bronchial segment is the third-generation airway and in this study is considered the proximal airway. This airway was dissected carefully and cleaned of lung parenchyma and pulmonary vessels under a binocular microscope. The proximal airway was dissected down to its first bifurcation. The middle third of this proximal airway was cut

---

ANTHONY J. MAZZEO, MD, EUGENE Y. CHENG, MD, Department of Anesthesiology, Medical College of Wisconsin, Froedtert Memorial Lutheran Hospital, 9200 W. Wisconsin Ave, Milwaukee, WI 53226, USA. ZELJKO J. BOSNJAK, PHD, Departments of Anesthesiology and Physiology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA. ROBERT L. COON, PHD, Department of Anesthesiology, Medical College of Wisconsin, Zablocki Veterans Administration Medical Center, 5000 W. National Ave, Milwaukee, WI 53295, USA. JOHN P. KAMPINE, MD, PHD, Department of Anesthesiology, Medical College of Wisconsin, John L. Doyne Hospital, 8700 W. Wisconsin Ave, Milwaukee, WI 53226, USA. Accepted for publication: January 18, 1996.

Correspondence to A.J.M.

sequentially into 2-mm segments (od 4–6 mm) that excluded side branches. This section of the proximal airway was chosen because it gave the most uniform outer diameter. These segments were then mounted on two tungsten wires (od 0.1 mm), each shaped into an isosceles triangle with the base passing through the lumen.

The distal airway was also selected from the same animal. This airway, obtained after the fifth or sixth bifurcation from the trachea, was dissected carefully and cleaned of lung parenchyma and pulmonary vessels. The airway after the fifth or sixth bifurcation, corresponding to the fifth and sixth airway generation, respectively, was selected based on which airway generation had an outer diameter closest to 1.0 mm. The distal airway was also cut sequentially into 2-mm segments (od 0.7–1.8 mm) that excluded side branches. Based on outer diameter [9] and histology on randomly selected 1-mm segments, these airways were considered bronchioli. These distal segments were then mounted on tungsten wires as described for the proximal airway. During placement of the wires, special care was taken not to damage the luminal surface.

The mounted bronchi and bronchioli were suspended in jacketed baths, temperature controlled at 37 °C. The apex of one triangle was fixed at a point located at the bottom of the bath and the apex of the other triangle was attached to a force transducer (Grass Model FT103, Grass Instruments, Quincy, MA, USA) for measurement of isometric force. All responses were measured by the force transducer and are reported as isometric tension in grams. These rings were then allowed to equilibrate at 37 °C for 1 h in baths containing a 15-ml solution of Krebs–Ringer bicarbonate of the following composition (mmol litre^{-1}): glucose 11.1; NaCl 118.3; KCl 4.7; $CaCl_2$ 2.5; $MgSO_4$ 1.2; KH_2PO_4 1.2; $NaHCO_3$ 28.0; and Ca^{2+} disodium edetate 0.026. This solution was aerated with 95 % oxygen and 5 % carbon dioxide to maintain pH 7.40 with a $P\text{CO}_2$ of 5.3 kPa and $P\text{O}_2$ greater than 66.7 kPa. These values were assessed by radiometric (ABL 30 Radiometer; Copenhagen, Denmark) methods and verified before electrical field stimulation, before construction of the dose-reponse curve, during the ED_{50} response, and during desflurane or halothane administration. In addition, $P\text{CO}_2$, $P\text{O}_2$ and anaesthetic concentrations were monitored continuously by an infrared absorption technique (Poet II, Criticare Systems Incorporated, Waukesha, WI, USA, for halothane and Datex Capnomac, Tewksbury, MA, USA, for desflurane). No residual halothane administrated from the initial procurement of the lung tissue was detected from the infrared absorption technique at this time. A minimum of 3 h elapsed from the time of tissue procurement to the tissue equilibration, which would be sufficient for any unmeasurable halothane to be dissipated.

DETERMINATION OF OPTIMAL LENGTH

Optimal length of the airway was determined by the response to transmural nerve stimulation after incremental changes in airway smooth muscle length. For transmural nerve stimulation, two platinum-plate eletrodes were placed parallel to the airway ring (1 cm distance between the electrodes). Electrical impulses were generated by a high current constant voltage stimulator (designed and tested by the Biomedical Engineering Section, Department of Anesthesiology, Medical College of Wisconsin, WI, USA). Based on preliminary experiments, the variables of the voltage stimulator used in this study (15 V, 0.5 ms, 25 Hz) produced maximal indirect airway smooth muscle contraction. This maximal response was abolished by atropine 1 µmol litre^{-1}, indicating that the contraction was not a result of direct electrical stimulation of the muscle [10].

The airway rings were allowed to equilibrate for 1 h after mounting in the jacketed baths. The airway rings were stretched progressively every 10 min, by 0.5-g increments for the proximal airway and 0.25-g increments for the distal airway, until the contractile response to a standard electrical stimulus (15 V, 0.5 ms, 25 Hz) of 30 s duration was maximal. The maximum response was obtained when two consecutive readings were equal. When this maximal response was reached, the airway ring was considered to be at optimal length.

After an additional hour of equilibration, resting tension at optimal length was measured. To block ganglionic nicotinic receptors, hexamethonium chloride 10 µmol litre^{-1} was then added to each bath and allowed to equilibrate for 30 min before acetylcholine challenge [11].

ACETYLCHOLINE AND ANAESTHETIC DOSE–RESPONSES

Acetylcholine cumulative dose–response curves were obtained for both proximal and distal airways by increasing the concentration in log increments every 2 min [12]. The dose range for the proximal airway was 0.01 µmol litre^{-1} to 10 mmol litre^{-1}, and 0.01 µmol litre^{-1} to 1 mmol litre^{-1} for the distal airway. The dose required to reach the maximal plateau response determined the maximum dose (ED_{max}) required for each airway group. After obtaining the maximal response in each tissue, a minimum of three bath rinses were performed to wash out the acetylcholine. The tissue rings were allowed to reach baseline resting tension and equilibrate for at least 1 h. The ED_{50} was calculated from the linear portion (20–80 % of maximum response) of the dose–response curve by linear regression analysis. This dose was then administered to each tissue to obtain a baseline control response before administration of anaesthetic. The control response to the ED_{50} was allowed to stabilize for 10 min.

After stabilization, the halothane or desflurane dose, equivalent to 0.9, 1.9 or 2.8 dog MAC, was selected randomly and allowed to equilibrate in each bath for a minimum of 15 min. After the response stabilized or the minimum equilibration time elapsed, whichever was longer in duration, the response was measured. The anaesthetic vaporizer was then turned off and the tissue was allowed a wash-out period of at least 15 min. A calibration curve with carrier gas flows (oxygen, carbon dioxide) and volatile anaesthetic concentrations used for the

Table 1 Characteristics of proximal and distal airway smooth muscle (mean (SD))

	Desflurane		Halothane	
	Proximal	Distal	Proximal	Distal
od (mm)	5.1 (0.5)	1.1 (0.3)	4.8 (1.4)	1.1 (0.8)
Applied length (mm)	3.6 (0.5)	1.2 (0.3)	4.1 (1.7)	1.8 (1.9)
Optimal length (mm)	8.7 (0.8)	2.3 (0.8)	8.9 (1.4)	2.9 (2.6)
Resting tension (g)	0.28 (0.32)	0.14 (0.11)	0.29 (0.23)	0.14 (0.05)
Response to EDmax of acetylcholine (g)	5.00 (1.27)	1.91 (0.56)	5.34 (0.65)	1.92 (0.45)
Response to ED_{50} of acetylcholine (g)	2.50 (1.83)	0.85 (0.50)	2.37 (0.91)	0.99 (0.56)
ED_{50} acetylcholine (μmol $litre^{-1}$)	40.3 (32.5)	5.4 (7.9)	26.2 (24.3)	1.9 (1.2)

Table 2 Responses to the ED_{50} of acetylcholine for proximal and distal airway smooth muscle before and after recovery from halothane and desflurane (mean (SD) percentage of maximal contraction)

Anaesthetic	Concentration	Airway	Pre-anaesthetic	Post-anaesthetic
Halothane	0.9 MAC	Proximal	40.6 (1.5)	39.4 (2.2)
	1.9 MAC		41.9 (2.2)	38.3 (1.6)
	2.8 MAC		45.4 (2.3)	40.3 (2.4)
	0.9 MAC	Distal	48.9 (1.3)	48.1 (2.2)
	1.9 MAC		47.7 (2.7)	48.9 (3.1)
	2.8 MAC		48.6 (1.5)	50.7 (1.8)
Desflurane	0.9 MAC	Proximal	49.0 (2.3)	49.9 (3.4)
	1.9 MAC		47.1 (2.1)	47.9 (2.8)
	2.8 MAC		48.9 (2.4)	47.9 (3.2)
	0.9 MAC	Distal	45.3 (2.6)	43.6 (2.7)
	1.9 MAC		44.3 (2.7)	43.9 (3.1)
	2.8 MAC		44.8 (3.3)	43.5 (3.5)

experiments were determined and correlated with gas chromatography samples and infrared absorption analyser (Poet II for halothane or Datex for desflurane) measurements. The infrared absorption measurements correlated with gas chromatography samples after these values (mmol $litre^{-1}$) were converted to percentage volume values. The infrared absorption measurements were than used to ensure stable anaesthetic concentrations in the baths throughout the experiments. The infrared absorption analyser intake sampler located in-line with the carrier gas showed that the anaesthetic concentrations in the baths equilibrated in less than 5 min. One dog MAC of halothane is equivalent to 0.88% [13] and 1 dog MAC of desflurane is equivalent to 7.2% [14].

DATA ANALYSIS

The control response for each ring was isometric contraction to the ED_{50} of acetylcholine before administration of the anaesthetic. Airway smooth muscle relaxation was the change in tension caused by the anaesthetic. This change was expressed as a percentage of the control response. Analysis of variance was performed on the control response to the ED_{50} of acetylcholine, expressed as a percentage of maximal contraction, between the proximal and distal airway, for each volatile anaesthetic and anaesthetic dose, to confirm that there was no significant difference between the control responses in both tissue groups. The control response to the ED_{50} of acetylcholine was also compared with the post-control response to the ED_{50} of acetylcholine using the paired *t* test to evaluate potential tissue deterioration or residual anaesthetic effect. To evaluate the differences between proximal and distal airway responses at each anaesthetic dose within an anaesthetic group, paired *t* tests were used.

Analysis of variance with Scheffé's test was used to test for significant differences between halothane and desflurane, the three concentrations of each anaesthetic and the tissue groups. $P < 0.05$ was considered significant. The results are expressed as mean (SD).

Results

To reach optimal length with the use of micromanipulators, the proximal airway required 1.0–3.5 g of applied tension and the distal airway 0.50–2.0 g. The average increase in length (3.8 (0.8) mm) needed to reach optimal length in the proximal airway was almost equal to the od (5.0 (0.4) mm). This finding was consistent with that of Stephens, Meyers and Cherniack [15]. The increase in length (1.6 (0.7) mm) needed to reach optimal length in the distal airway was slightly greater than the od (1.0 (0.4) mm). The resting tension of the proximal airway (0.29 (0.12) g) was twice the resting tension of the distal airway (0.13 (0.04) g) (table 1).

The maximum effective dose (ED_{max}) of acetylcholine, the dose required for a plateau response, was 10 mmol $litre^{-1}$ for the proximal airway and 1 mmol $litre^{-1}$ for the distal airway. The physical characteristics of the proximal and distal airways in each anaesthetic group are presented in table 1. The control responses to the ED_{50} of acetylcholine, expressed as a percentage of maximal contraction, were not significantly different between the proximal and distal airways in each anaesthetic group (table 2). This indicates that each airway group was contracted

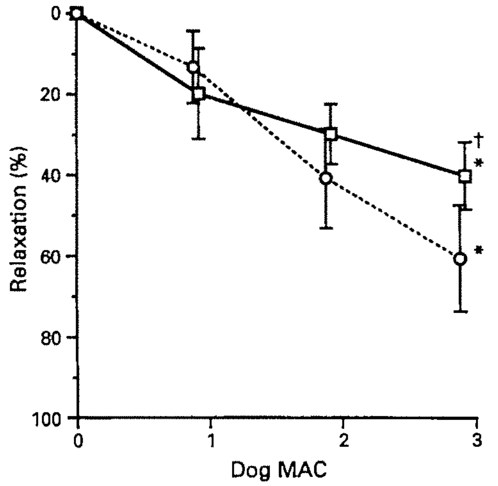


Figure 1 Percentage relaxation of proximal (third-generation) airway smooth muscle pre-contracted with the ED_{50} of acetylcholine at 0.9, 1.9, and 2.8 dog minimum alveolar anaesthetic concentration (MAC) of desflurane (○) and halothane (□). $*P < 0.05$ *vs* 0.9 MAC; $\dagger P < 0.05$ *vs* desflurane.

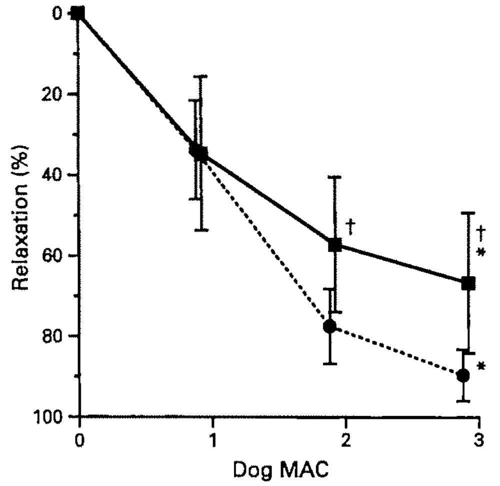


Figure 2 Percentage relaxation of distal (fifth- and sixth-generation) airway smooth muscle pre-contracted with the ED_{50} of acetylcholine at 0.9, 1.9, and 2.8 dog minimum alveolar anaesthetic concentration (MAC) of desflurane (●) and halothane (■). $*P < 0.05$ *vs* 0.9 MAC; $\dagger P < 0.05$ *vs* desflurane.

to the same extent before administration of anaesthetic. The post-experimental responses to the ED_{50} of acetylcholine were not significantly different from their respective control values, indicating that no tissue deterioration occurred and the anaesthetic effect was reversible.

There was a significant difference between the relaxant effects of 0.9, 1.9 and 2.8 MAC for both desflurane and halothane (figs 1, 2) in the proximal and distal airway tissue groups, indicating a dose–response effect for these anaesthetics. Also, there was a significant difference between the relaxant effects of the proximal and distal airways at each anaesthetic dose within each anaesthetic group ($P < 0.003$) the average distal airway relaxed 50 % more than the proximal airway). Desflurane relaxed the proximal airway smooth muscle to a greater extent than halothane at 2.8 MAC ($P = 0.0001$) and the distal airway smooth muscle at 1.9 ($P = 0.0007$) and 2.8 MAC ($P = 0.002$). The proximal airway smooth muscle relaxed 13 %, 41 % and 61 % with desflurane and 20 %, 29 % and 41 % with halothane at 0.9, 1.9 and 2.8 MAC, respectively. The distal airway smooth muscle relaxed 34 %, 78 % and 90 % with desflurane and 35 %, 57 % and 67 % with halothane at 0.9, 19 and 2.8 MAC, respectively (figs 1, 2).

Discussion

This study demonstrated that volatile anaesthetics (desflurane and halothane) had a greater bronchodilator effect on distal airway smooth muscle than on the more proximal airway smooth muscle in a dose-dependent manner, similar to the effects of isoflurane [7]. Furthermore, we found that desflurane had a greater direct bronchodilator effect than halothane at the doses tested (greater than 1 MAC for the distal airway smooth muscle and greater than 2 MAC for the proximal airway smooth muscle). Therefore, desflurane had good direct bronchodilator effects on the intraparenchymal airway despite its association with coughing and laryngospasm on induction [1].

To compare the proximal airway, which has a larger diameter and more muscle mass, to the distal airway, isometric tension was measured, thereby allowing the diameter of the airway ring to remain constant. Under these circumstances, changes in tension would be linearly proportional. In addition, the airway smooth muscle rings were evaluated at optimal length. This enables each airway to be compared at the same point on the length–tension curve. Furthermore, the ED_{50} of acetylcholine for each individual tissue was used as the baseline for comparison. This response maintains each tissue at the same degree of activation and contraction. The ED_{50} response, when expressed as a percentage of the EDmax response, reflects the effects of functional muscle tissue so that it is not necessary to take into account the mass of the tissue.

It is possible that the increased ED_{50} of acetylcholine in the proximal airway was caused by cartilage. However, the ED_{50} of acetylcholine between airways with and without papain-softened cartilage were not found to be different [16]. Also, isometric tension measured in bronchial smooth muscle with cartilage compared with bronchial smooth muscle with the cartilage removed was not significantly different [17]. This suggests that the presence of cartilage does not oppose contraction. Furthermore, cartilage does not oppose relaxation but may actually facilitate it. When airway smooth muscle is contracted, cartilage plates and collagen fibres between these plates frequently reverse their orientation by almost 180° [18]. This orientation and the elastic nature of cartilage results in a tendency to spring outward, as described by Olsen and colleagues [18]. Agents that relax airway smooth muscle such as volatile anaesthetics would then allow the cartilage to spring outward, facilitating the tendency for relaxation. Despite this tendency, the distal airway, which lacks cartilage, relaxed to a greater extent than the proximal airway.

To minimize the difference in gas diffusion time, lung parenchyma and vascular tissues were removed carefully and the airway rings were cut into small segments. In addition, airway smooth muscle was allowed to equilibrate with the anaesthetic for a minimum of 15 min, or until the tissue response stabilized, to ensure that each tissue reached the same anaesthetic saturation point. Therefore, the effects on airway smooth muscle contraction could be normalized and compared.

Previous studies have examined the bronchodilator effect of anaesthetics by conventional techniques, such as measuring lung resistance (RL) *in vivo* [19–21], a value indicative of proximal airway resistance [22], or by *in vitro* techniques, such as measuring isometric force [11, 23, 24]. The results of these studies have shown that the indirect [21, 23, 24] and direct effects [11, 19, 20, 25] of anaesthetics are responsible for bronchodilatation. Warner and colleagues, using aerosolized acetylcholine, examined the direct effects of halothane on changes in pulmonary resistance and found a decrease in pulmonary resistance at 1.2 MAC from a baseline value of 6.32 to 4.85 $\text{cm H}_2\text{O litre}^{-1}\text{ s}^{-1}$ (23% change). Hirshman and colleagues [20], using an aerosolized cholinergic agonist, also found a reduction in pulmonary resistance as a result of halothane in the Basenji–Greyhound dog model of asthma. In a study measuring both airway smooth muscle tension and intracellular Ca^{2+} in canine trachea, Jones and colleagues [25] found that halothane reduced both of these variables. Halothane was also found to suppress tracheal smooth muscle contractions produced by direct muscle stimulation and increase the threshold for muscle activation [26].

In vivo studies have evaluated variations in global lung resistance (RL), which is indicative of changes in the more proximal airway and may be insensitive to changes in the more distal airway [21]. In addition, RL is a function of airway resistance and tissue resistance, with tissue resistance being the principal component of RL [27]. However, it has been shown that RL can be used as an index of changes in airway calibre [27], although it is not known if this index is homogeneous throughout the lung. Studies performed *in vitro* examined the direct effects of anaesthetics on the trachea and in some, only as far distally as the segmental bronchus. The results of these *in vivo* and *in vitro* studies indicated that volatile anaesthetics have a significant bronchodilator effect on proximal airway smooth muscle [11, 19, 20, 21]. Furthermore, the effects of 1 MAC of halothane may depress neural transmission and smooth muscle to an equal extent [19].

The clinical importance of the direct bronchocontraction effects of volatile anaesthetics on airway smooth muscle may be more important than previously thought. Earlier studies focused on the direct effects of anaesthetics on the larger, more proximal, airway rather than the distal airway, which is the main contributor to airway resistance. However, in a more recent study, Brown, Zerhouni and Hirshman [28], using high resolution computer tomography, examined the effects of isoflurane and halothane on proximal and distal airways constricted with histamine. Their data suggested that administration of isoflurane and halothane (> 1.1 MAC) resulted in greater bronchodilatation in airways less than 3 mm compared with airways greater than 7 mm. Mazzeo and colleagues confirmed that the volatile anaesthetic isoflurane had a differential effect on airway smooth muscle and that the distal airway smooth muscle was significantly more sensitive to the bronchodilating effects of isoflurane [7]. In this study, we also demonstrated that desflurane and halothane *in vitro* had a similar heterogeneous effect on airway smooth muscle.

The increased bronchodilator effect in the distal airway could be a result of several possibilities. This differential effect could be caused by structural or physiological differences, or both, in the bronchus compared with the bronchiolus. Further investigations are needed to define the factors involved in the differential effect of anaesthetics on airway smooth muscle and the greater relaxant effect of desflurane on airway smooth muscle in general. Discovering the reason for the differential effect of anaesthetics may help to develop a better understanding of anaesthetic actions on airway smooth muscle in the normal patient and in those with bronchospastic disease. This understanding may also lead to improvement and development of more rational drug therapies for the treatment of patients with reactive airway disease.

Acknowledgement

We thank Nordeana Nimphius for technical assistance and Dr Edward Zuperku for his assistance with the statistical analysis. This work was supported by Anesthesiology Research Training Grant GM 08377, Medical College of Wisconsin Institution Funding, and VA Medical Research Funds.

References

1. Warltier DC, Pagel PS. Cardiovascular and respiratory actions of desflurane: is desflurane different from isoflurane? *Anesthesia and Analgesia* 1992; **75**: S17–S31.
2. Pedley, TJ, Schroter, RC, Sudlow, MF. The prediction of pressure drop and variation of resistance within the human bronchial airways. *Respiration Physiology* 1970; **9**: 387–405.
3. Shioya T, Munoz NM, Leff AR. Effect of resting smooth muscle length on contractile response in resistance airways. *Journal of Applied Physiology* 1987: **62**: 711–717.
4. McNamara AE, Müller NL, Okazawa M, Arntorp J, Wiggs BR, Paré PD. Airway narrowing in excised canine lungs measured by high-resolution computed tomography. *Journal of Applied Physiology* 1992; **73**: 307–316.
5. Barnes PJ. Neural control of human airways in health and disease. *American Review of Respiratory Disease* 1986; **134**: 1289–1314.
6. Shioya T, Pollack ER, Munoz NM, Leff AR. Distribution of airway contractile responses in major resistance airways of the dog. *American Journal of Pathology* 1987; **129**: 102–117.
7. Mazzeo AJ, Cheng EY, Stadnicka A, Bosnjak ZJ, Coon RL, Kampine JP. Topographical differences in the direct effects of isoflurane on airway smooth muscle. *Anesthesia and Analgesia* 1994; **78**: 948–954.
8. Horsfield K, Cumming G. Morphology of the bronchial tree in dog. *Respiration Physiology* 1976; **26**: 173–182.
9. Evans HE, Christensen GC. The respiratory apparatus. In: Miller WS, ed. *Anatomy of the Dog*. Philadelphia: WB Saunders Company, 1980; 526–543.
10. Russell JA. Responses of isolated canine airways to electric stimulation and acetylcholine. *Journal of Applied Physiology* 1978; **45**: 690–698.

11. Sayiner A, Lorenz RR, Warner DO, Rehder K. Bronchodilation by halothane is not modulated by airway epithelium. *Anesthesiology* 1991; 75: 75–81.
12. Van Rossum JM. Cumulative dose–response curves. II. Technique for the making of dose–response curves in isolated organs and the evaluation of drug parameters. *Archives Internationales de Pharmacodynamie* 1963; **143**: 299–330.
13. Koblin DD, Eger EI, Johnson BH, Collins P, Harper MH, Ternell RC, Speers L. Minimum alveolar concentrations and oil/gas partition coefficients of four anesthetic isomers. *Anesthesiology* 1981; **54**: 314–317.
14. Dooley BM, Waters SJ, Terrell RC, Robinson JL. MAC of 1653 in beagle dogs and New Zealand white rabbits. *Anesthesiology* 1988; **69**: 89–91.
15. Stephens NL, Meyers JL, Cherniack RM. Oxygen, carbon dioxide, H^+ ion and bronchial length–tension relationships. *Journal of Applied Physiology* 1968; **25**: 376–383.
16. Moreno RH, Lisboa C, Hogg JC, Pare PD. Limitation of airway smooth muscle shortening by cartilage stiffness and lung elastic recoil in rabbits. *Journal of Applied Physiology* 1993; 75: 738–744.
17. Jiang HE, Stephens NL. Contractile properties of bronchial smooth muscle with and without cartilage. *Journal of Applied Physiology* 1990; **69**: 120–126.
18. Olsen CR, Stevens AE, Pride NB, Staub NC. Structural basis for decreased compressibility of constricted tracheae and bronchi. *Journal of Applied Physiology* 1967; **23**: 35–39.
19. Warner DO, Vettermann J, Brichant J-F, Rehder K. Direct and neurally mediated effects of halothane on pulmonary resistance in vivo. *Anesthesiology* 1990; **72**: 1057–1063.
20. Hirshman CA, Edelstein G, Peetz S, Wayne R, Downes H. Mechanism of action of inhalational anesthesia on airways. *Anesthesiology* 1982; **56**: 107–111.
21. Shah MV, Hirshman CA. Mode of action of halothane on histamine-induced airway constriction in dogs with reactive airways. *Anesthesiology* 1986; **65**: 170–174.
22. Moreno RH, Hogg JC, Paré PD. Mechanics of airway narrowing. *American Review of Respiratory Disease* 1986; **133**: 1171–1180.
23. Brichant J-F, Gunst SJ, Warner DO, Rehder K. Halothane, enflurane, and isoflurane depress the peripheral vagal motor pathway in isolated canine tracheal smooth muscle. *Anesthesiology* 1991; **74**: 325–332.
24. Yamakage M. Direct inhibitory mechanisms of halothane on canine tracheal smooth muscle contraction. *Anesthesiology* 1992; **77**: 546–553.
25. Jones KA, Wong GY, Lorenz RR, Warner DO, Sieck GC. Effects of halothane on the relationship between cytosolic calcium and force in airway smooth muscle. *American Journal of Physiology* 1994; **266**: L199–204.
26. Korenaga S, Takeda K, Yushi I. Differential effects of halothane on airway nerves and muscle. *Anesthesiology* 1984; **60**: 309–318.
27. Warner DO, Vettterman J, Brusasco V, Rehder K. Pulmonary resistance during halothane anesthesia is not determined only by airway caliber. *Anesthesiology* 1989; **70**: 453–460.
28. Brown RH, Zerhouni EA, Hirshman CA. Comparison of low concentrations of halothane and isoflurane as bronchodilators. *Anesthesiology* 1993; **78**: 1097–1101.

British Journal of Anaesthesia 1996; **76**: 847–853

Halothane and potassium channels in airway smooth muscle

T. FUKUSHIMA, A. HIRASAKI, K. A. JONES AND D. O. WARNER

Summary

Earlier studies have suggested that halothane may relax smooth muscle in part by opening adenosine triphosphate-sensitive potassium (K_{ATP}) channels. We tested this hypothesis *in vitro* by examining the interaction of halothane with glibenclamide, a K_{ATP} channel blocker, and YM934, a K_{ATP} channel opener, in strips of canine tracheal smooth muscles mounted in an organ bath system. To examine the specificity of any effects of halothane on the K_{ATP} channel, we assessed the interaction of halothane with tetraethylammonium (TEA), an antagonist of the large-conductance, calcium-activated potassium channel. Experiments were conducted with drugs added before exposure to increasing concentrations of acetylcholine (ACh), and with drugs added after stable increases in force produced by ACh were achieved (ACh precontraction). Exposure to halothane 0.62 mmol litre^{-1} (equivalent to approximately 2 MAC) increased significantly the ED_{50} for ACh-induced contractions (by 0.24 (SEM 0.07) µmol litre^{-1}). TEA 1 mmol litre^{-1} but not glibenclamide 10 µmol litre^{-1} significantly augmented this increase in ED_{50} (by an additional 0.17 (0.06) µmol litre^{-1}). In strips precontracted with ACh, TEA, but not glibenclamide, potentiated concentration-dependent relaxation induced by halothane. Incubation with YM934 0.32 µmol litre^{-1} increased significantly the ED_{50} for ACh-induced contractions (from 0.12 (0.02) to 0.55 (0.11) µmol litre^{-1}), an increase not affected by exposure to halothane 0.72 mmol litre^{-1}. When added to strips precontracted with approximately ACh 0.3 µmol litre^{-1}, YM934 produced concentration-dependent relaxation; halothane had little effect on this relaxation. These results do not support the hypothesis that halothane relaxes canine tracheal smooth muscle in part by opening K_{ATP} channels. (*Br. J. Anaesth.* 1996; **76**: 847–853)

Key words

Anaesthetics volatile, halothane. Lung, trachea. Ions, potassium. Ions, ion channels. Airway, muscles.

Halothane is a potent bronchodilator, relaxing airway smooth muscle both by depressing neural pathways innervating the muscle and by a direct effect on the smooth muscle cell [1, 2]. One proposed mechanism for this effect is a decrease in intracellular calcium concentration [3, 4], produced in part by depression of calcium influx via voltage-sensitive calcium channels in the sarcolemma. Under voltage-clamped conditions, halothane depresses the function of these channels in several types of cells [5], including vascular smooth muscle [6, 7]. Changes in membrane potential could also affect calcium channel function. Hyperpolarization of the cell membrane has been suggested as a mechanism for anaesthetic action in several cell types [8], including airway smooth muscle [9]. One mechanism that could produce hyperpolarization would be an increase in conductance of potassium channels [10]. In support of such a mechanism in airway smooth muscle, Mehr and Lindeman [11] found that glibenclamide, an antagonist of adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channels, abolished the ability of halothane to decrease airway responsiveness to hypocapnia in a canine model of asthma. Evidence for activation of potassium channels has been reported for several other types of cells, including activation of the K_{ATP} channel in vascular smooth muscle [12]. However, there is also considerable evidence that halothane depresses the function of several types of potassium channels [6, 7, 13–15], although the K_{ATP} channel has not been examined specifically.

The purpose of this study was to test the hypothesis that halothane relaxes airway smooth muscle *in vitro*, in part by activation of K_{ATP} channels. We examined the interaction of halothane with glibenclamide and YM934, a K_{ATP} channel opener [16], during stimulation of isolated strips of canine tracheal smooth muscle with acetylcholine (ACh). To determine the specificity of any effects of halothane on the K_{ATP} channel, we also examined the interaction of halothane with tetraethylammonium (TEA), an antagonist of the large-conductance, calcium-activated potassium (K_{Ca}) channel.

Materials and methods

TISSUE PREPARATION

The trachea was removed from 45 mongrel dogs anaesthetized with pentobarbitone and exsanguinated. The tissue was immersed immediately in a chilled physiological salt solution (PSS) of the following composition (mmol litre^{-1}): $MgSO_4$ 0.8, KH_2PO_4 1.2, KCl 3.4, $CaCl_2$ 2.4, NaCl 110,

---

TOMIHIRO FUKUSHIMA*, MD, AKAHITO HIRASAKI, MD, KEITH A. JONES, MD, DAVID O. WARNER†, MD, Departments of Anesthesiology and of Physiology and Biophysics, Mayo Clinic and Mayo Foundation, Rochester, MN 55905, USA. Accepted for publication: January 12, 1996.

*Present address: 252 Nishiichi No. 202, Okayama City, Japan 700.

†Address for correspondence: Department of Anesthesiology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.

$NaHCO_3$ 25.7 and glucose 5.6. After removal of the epithelium and connective tissue, rectangular strips of smooth muscle (10–15 mm long and 2 mm wide) were dissected from the middle of the trachea. Each strip was suspended vertically in a 25-ml water-jacketed tissue bath containing PSS at 37 °C and bubbled with 94% oxygen–6% carbon dioxide, providing a pH of 7.4, Po_2 of 73 kPa and Pco_2 of 4.8 kPa (Instrumentation Laboratories model 1302). The strips were connected to strain gauges (Grass FT03) for isometric force recording (Hewlett-Packard 7418A). Indomethacin 10 μmol litre^{-1} was added to all baths.

The strips were washed in PSS for approximately 2 h while being stimulated supramaximally (0.5-ms pulse duration, 25 Hz, 15 V) by electrical field stimulation at 5-min intervals. Muscle length was increased after each contraction until the force of contraction reached a maximum. Each strip was maintained at this optimal length for the duration of the experiment. The contractile response to ACh 100 μmol litre^{-1}, defined as the maximal response, was then determined.

EXPERIMENTAL DESIGNS

Because different mechanisms are involved in the induction compared with the maintenance of force in airway smooth muscle [17], experiments were conducted both with drugs added before exposure to increasing concentrations of ACh, and with drugs added after stable increases in force produced by ACh were achieved (ACh precontraction).

Interpretation of precontraction experiments is complicated by the fact that the amount of relaxation produced by an antagonist of contraction may depend on both the initial force and the concentration of contractile agonist needed to produce that force (a phenomenon referred to as functional antagonism). In some experiments, prior exposure to a compound with effects on muscle contractility (e.g. halothane) changes the initial force of contraction produced for a given concentration of ACh. In the case of halothane, such an effect is observed even at maximal concentrations of ACh [18]. In these instances, options include maintaining a constant ACh concentration and allowing the initial force to vary, or manipulating ACh concentration to keep the initial force constant between experimental conditions. We chose the latter option, as described below. However, when the ACh concentration needed to produce equal initial forces differed significantly between conditions, we also performed additional experiments, using these different ACh concentrations and allowing initial forces to vary, to determine if functional antagonism was responsible for the observed results.

Four series of experiments were performed, evaluating: (1) the effects of K^+-channel block produced by TEA 1 mmol litre^{-1} or glibenclamide 10^{-5} mol litre^{-1} on the ability of 1.7% halothane to inhibit force developed in response to cumulative increases in ACh concentrations; (2) the effects of K^+-channel block on the ability of halothane to relax strips precontracted with ACh to approximately 50% of maximal force; (3) the effect of 1.7% halothane pretreatment on the ability of YM934, a K_{ATP} channel opener, to inhibit force developed in response to cumulative increases in ACh concentrations; and (4) the effects of halothane on the ability of YM934 to relax strips precontracted with ACh to approximately 50% of maximal force. When appropriate, control experiments were performed with the vehicle used to solubilize glibenclamide (4×10^{-5} vol% dimethylsulphoxide (DMSO)). In all experiments using ACh precontraction, another strip paired for each experimental condition was used to control for any effects of time on the level of precontraction [1].

DATA ANALYSIS

Isometric forces were expressed as a percentage of the maximal force (for ACh concentration–response procedures) or as a percentage of the initial force (for ACh precontraction procedures). In strips precontracted with ACh, the contractile responses were adjusted for the effect of time [1] according to the formula:

$$C_t = (C_1/C_2)\,C_d$$

where C_t = the time-adjusted response, C_1 = response of time-control muscle (initial measurement), C_2 = response of time-control muscle (measured in parallel with the exposed muscle) and C_d = response of the muscle exposed to drug.

Sigmoidal concentration–response curves to ACh or YM934 were analysed using the method of Meddings, Scott and Fick [19]. In this method, force (F) at any concentration of drug (C) is given by the equation:

$$F = F_m\,C/(\mathrm{ED}_{50} + C)$$

where F_m = maximal (or minimal) force and ED_{50} = concentration that produces the half-maximal (or minimal) force for that drug. Non-linear regression analysis was used to fit values of F_m and ED_{50} to data for F and C for each condition studied. This method allows comparison of curves to determine if they are significantly different, and if this overall difference can be attributed to differences in F_m, ED_{50}, or both.

The potency of halothane in relaxing strips precontracted with ACh was quantified by linear regression of the relationship between force and halothane concentration. To test for differences in potency between conditions, slopes were compared by one-way analysis of variance (ANOVA), with *post hoc* comparisons performed using the Student–Newman–Keuls method.

Data are expressed as mean (SEM). $P < 0.05$ was considered significant. In all cases n represents the number of pairs of strips analysed for a given experimental condition. For a given condition, each pair of strips was obtained from a different dog.

DRUGS

Halothane (Ayerst Laboratories) was added to the aerating gas mixture via an on-line vaporizer. The concentration of halothane in the gas mixture was monitored continuously by a mass spectrometer (model MGA-1100, Perkin–Elmer). The concentration of halothane in the PSS was determined by gas chromatography (model 5880A, Hewlett-Packard). The drugs used were ACh hydrochloride, indomethacin (Sigma), tetraethylammonium chloride, glibenclamide (Research Biochemicals) and YM934 (Yamanouchi Pharmaceuticals). Drug concentrations are expressed as final bath concentrations of the salts.

Results

EFFECTS OF HALOTHANE AND K$^+$-CHANNEL ANTAGONISTS ON THE ACH CONCENTRATION–RESPONSE RELATIONSHIP

Exposure to TEA 1 mmol litre^{-1} increased significantly the maximal force developed in response to cumulative increases in ACh concentration (from 94.7 (1.8)% to 108.1 (1.8)% of the initial maximal force; $P < 0.05$ by non-linear regression) without changing significantly the ED_{50} concentration of ACh (from 0.33 (0.04) to 0.29 (0.03) µmol litre^{-1}) (fig. 1), that is TEA increased maximal force developed in response to ACh but did not change the sensitivity of the strips to ACh. Exposure to glibenclamide 10 µmol litre^{-1} did not change significantly the ACh concentration–response relationship (change in maximal force from 96.7 (1.7)% to 101.4 (1.6)% and change in ED_{50} from ACH 0.21 (0.02) to 0.18 (0.03) µmol litre^{-}) (fig. 2.).

Exposure to 1.7% halothane increased significantly the ED_{50} concentration of ACh in strips not incubated with a K$^+$-channel antagonist (control, $P < 0.05$), and in strips incubated with TEA 1 mmol litre^{-1} or glibenclamide 10 µmol litre^{-1} (figs 1, 2; $P < 0.05$). The increase in ED_{50} produced by halothane was significantly greater in strips incubated with TEA compared with control strips (increases of ACh 0.41 (0.09) and 0.24 (0.07) µmol litre^{-1}, respectively; $P = 0.016$ by paired t test), demonstrating that TEA potentiated the effect of halothane on the sensitivity of the strips to ACh. However, the increase in ED_{50} produced by halothane was not significantly different in strips incubated with glibenclamide compared with control strips (increases of ACh 0.19 (0.06) and 0.15 (0.04) µmol litre^{-1}, respectively; ns by paired t test). Halothane did not significantly change the maximal force under any conditions.

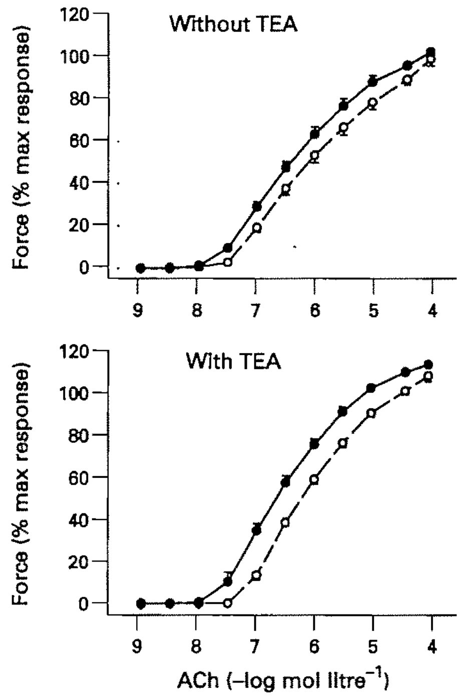


Figure 1 Active isometric force developed in response to increasing concentrations of acetylcholine (ACh) in strips exposed (○) or not exposed (●) to halothane 0.62 (0.02) mmol litre^{-1} (equal to approximately 2 MAC in the gas phase). Strips in the lower panel were incubated with tetraethylammonium chloride (TEA) 1 mmol litre^{-1} for 20 min before exposure to ACh. At this concentration, TEA predominantly affects the K_{Ca} channel, with little if any effect on delayed rectifier potassium channels in airway smooth muscle [20]. Values are mean, SEM, for six experiments.

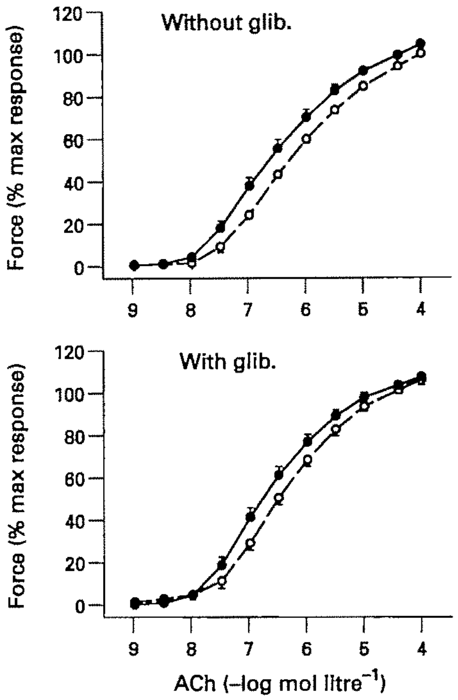


Figure 2 Active isometric force developed in response to increasing concentrations of acetylcholine (ACh) in strips exposed (○) or not exposed (●) to halothane 0.62 (0.02) mmol litre^{-1}. Strips in the lower panel were incubated with glibenclamide 10^{-5} mol litre^{-1} for 20 min before exposure to ACh. Values are mean, SEM, for six experiments.

EFFECTS OF K-CHANNEL ANTAGONISTS ON HALOTHANE-INDUCED RELAXATION

Precontraction of strips to approximately 50% of maximal force required a significantly lower concentration of ACh in strips incubated with TEA 1 mmol litre^{-1} (ACh 0.19 (0.04) µmol litre^{-1}) compared with control strips (ACh 0.33 (0.07) µmol litre^{-1}; $P < 0.02$ by paired t test). ACh concentrations for strips incubated with glibenclamide 10 µmol litre^{-1} (ACh 0.24 (0.06) µmol litre^{-1}) did not differ significantly from those required in control strips. The actual forces achieved were 48.1 (0.5)%, 49.3 (0.8)% and 48.6 (0.5)% of maximal force for control, TEA- and glibenclamide-treated strips, respectively.

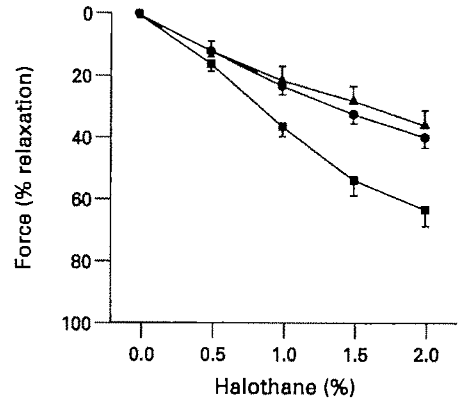


Figure 3 Relationship between force and halothane concentration in gas aerating the tissue bath in strips precontracted with acetylcholine to approximately 50 % of maximal force. Data for strips not exposed to potassium channel antagonists (control, ●), strips incubated with tetraethylammonium chloride (TEA) 1 mmol litre^{-1} (■) and strips incubated with glibenclamide 10^{-5} mol litre^{-1} (▲) are shown. Halothane concentrations achieved in the tissue baths were 0.23 (0.01), 0.41 (0.01), 0.54 (0.02) and 0.70 (0.03) mmol litre^{-1} for 0.5 %, 1.0 %, 1.5 % and 2 % halothane added to the gas aerating the baths, respectively. Values are mean, SEM, for eight experiments.

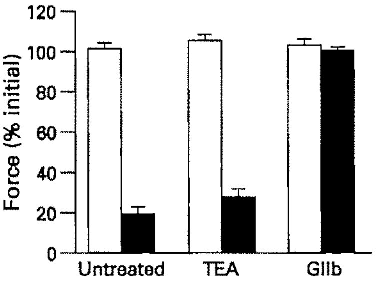


Figure 4 Effect of YM934 0.32 μmol litre^{-1} (■) on force in strips precontracted with acetylcholine to approximately 50 % of maximal force and incubated with tetraethylammonium chloride (TEA) 1 mmol litre^{-1}, glibenclamide 10 μmol litre^{-1} or neither (untreated). Force is expressed as a percentage of the force initially developed in response to ACh. Control strips (□) did not receive YM934 and represent controls for any effects of time. Values are mean, SEM, for eight experiments.

Halothane produced concentration-dependent relaxation of these precontracted strips (fig. 3) that could be quantified as the slope of a linear regression of force *vs* halothane concentration. The absolute value of this slope was significantly greater in strips incubated with TEA 1 mmol litre^{-1} compared with control strips (−33.8 (2.8) and −21.0 (1.7) % initial force × halothane^{-1}, respectively; $P < 0.05$ by ANOVA and Student–Neuman–Keuls test), indicating that TEA potentiated halothane-induced relaxation. Glibenclamide 10 μmol litre^{-1} did not significantly affect the slope of this relationship, indicating that glibenclamide did not affect the ability of halothane to relax the strips.

The K_{ATP} channel agonist YM934 was added to strips precontracted with ACh to 50 % of maximal force to assess the adequacy of K_{ATP} channel antagonism by glibenclamide 10 μmol litre^{-1} and the specificity of TEA. YM934 0.32 μmol litre^{-1} produced significant relaxation in control strips and strips treated with TEA 1 mmol litre^{-1} (fig. 4, $P < 0.05$ by ANOVA and Student–Neuman–Keuls). The amount of relaxation was not significantly different between control strips and strips treated with TEA 1 mmol litre^{-1}. However, glibenclamide 10 μmol litre^{-1} completely blocked this relaxation (fig. 4).

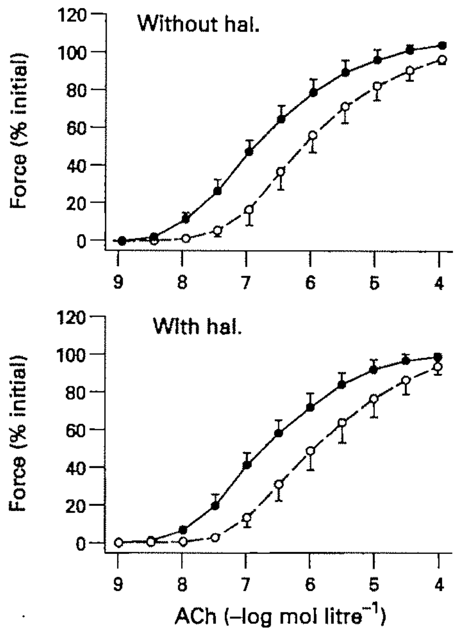


Figure 5 Force developed in response to increasing concentrations of acetylcholine (ACh) in strips exposed to YM934 0.32 μmol litre^{-1} (○) or to the vehicle used to solubilize YM934 (●). Strips in the lower panel were incubated with halothane 0.72 (0.04) mmol litre^{-1}. Values are mean, SEM, for five experiments.

Because TEA decreased significantly the ACh concentration required to produce approximately 50 % of maximal force (from 0.33 (0.07) μmol litre^{-1} to 0.19 (0.04) μmol litre^{-1}; $P < 0.01$), the ability of halothane to relax strips precontracted with these two concentrations of ACh was studied in separate experiments (in the absence of TEA, $n = 6$). The slopes of linear regressions of force *vs* halothane concentration did not differ between the two concentrations of ACh (−22.4 (1.6) and −24.2 (1.2) % initial force × % halothane^{-1}, respectively, $P = 0.09$), demonstrating that the potentiation of halothane-induced relaxation by TEA was not an artefact of functional antagonism. In other words, changes in the response to halothane produced by TEA could not be explained by the different ACh concentrations used to precontract TEA-treated and control strips.

EFFECTS OF HALOTHANE AND A K_{ATP} AGONIST ON THE ACH CONCENTRATION–RESPONSE RELATIONSHIP

Incubation with YM934 0.32 μmol litre^{-1} increased significantly the ED_{50} of ACh (from 0.12 (0.02) to 0.55 (0.11) μmol litre^{-1}; $P < 0.01$), demonstrating that YM934 decreased the sensitivity of the strips to ACh (fig. 5). Exposure to halothane 0.76 (0.04) mmol litre^{-1} did not affect significantly the increase in ED_{50} produced by YM934. YM934 did not change the maximal force developed in response to ACh under any condition. The vehicle used to

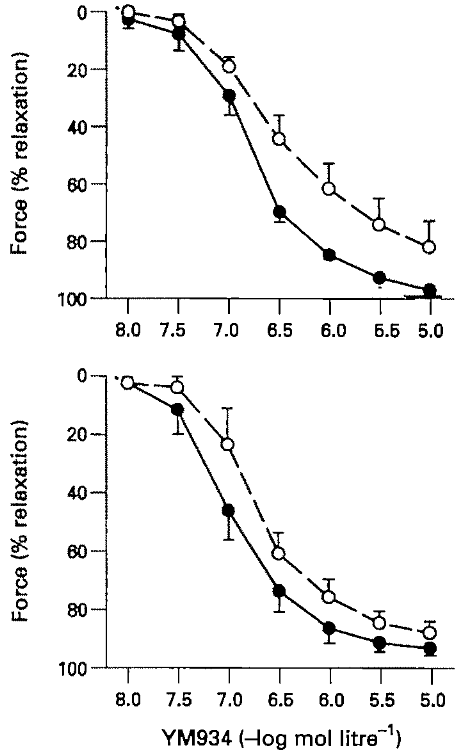


Figure 6 Top: Relationship between force and the concentration of YM934 in strips exposed (halothane, ○) or not exposed (control, ●) to halothane 0.76 (0.03) mmol litre^{-1}. ACh concentration was manipulated to produce an initial force of approximately 50 % maximal force. Values are mean, SEM for eight experiments. Bottom: Relationship between force and the concentration of YM934 in strips contracted with ACh 0.33 μmol litre^{-1} (○) or ACh 0.86 μmol litre^{-1} (●), values equal to the mean ACh concentrations used to precontract the control and halothane-treated strips, respectively, depicted above. Note the similar results to those above, suggesting much of the difference in YM934-induced relaxation depicted above can be accounted for by differences in ACh concentrations used to produce approximately equal initial forces. Values are mean, SEM, for six experiments.

dissolve YM934 did not significantly affect the ACh concentration–response relationship (data not shown).

EFFECT OF HALOTHANE ON RELAXATION PRODUCED BY A K_{ATP} CHANNEL AGONIST

Precontraction of the strips to approximately 50 % of maximal force required a significantly higher concentration of ACh in strips incubated with halothane 0.82 (0.04) mmol litre^{-1} (ACh 0.86 (0.15) μmol litre^{-1}) compared with control strips (ACh 0.33 (0.07) μmol litre^{-1}; $P = 0.0008$ by paired t test). When added to strips precontracted with ACh, YM934 produced a concentration-dependent relaxation (fig. 6 (top)). Halothane exposure significantly attenuated the maximal decrease in force produced by YM934 (from 1001 (3.0) to 83.6 (5.5) % of the initial force; $P < 0.05$ by non-linear regression), without significantly changing the ED_{50} of YM934 (0.19 (0.03) and 0.30 (0.09) μmol litre^{-1} for strips exposed and not exposed to halothane, respectively. The addition of the vehicle used to dissolve YM934 did not significantly affect force (data not shown).

Because halothane exposure increased significantly the ACh concentration required to produce approximately 50 % of maximal force (from 0.33 (0.07) to 0.86 (0.15) μmol litre^{-1}), the ability of YM934 to relax strips precontracted with these two concentrations of ACh was studied in separate experiments (without halothane exposure, $n = 6$). Increasing the ACh concentration used for precontraction significantly attenuated the maximal decrease in force produced by YM934 (from 96.8 (2.0) to 90.3 (2.5) % of the initial force; $P < 0.05$ by non-linear regression) without significantly changing the ED_{50} of YM934 (0.13 (0.01) and 0.21 (0.03) μmol litre^{-1} for strips contracted with ACh 0.33 μmol litre^{-1} and 0.86 μmol litre^{-1}, respectively). The changes in the maximal decrease in force and ED_{50} produced by halothane and by increases in precontraction ACh concentration did not differ significantly. Thus it appears that the difference in YM934-induced relaxation observed in figure 6 can be accounted for by differences in ACh concentrations used to produce approximately equal initial forces.

Discussion

The principal findings of this study were that there was no interaction between halothane and a blocker of the K_{ATP} channel in their effects on force in isolated canine airway smooth muscle during stimulation with ACh, and that halothane had little effect on the ability of a K_{ATP} channel opener to relax airway smooth muscle. These findings do not support the hypothesis that halothane relaxes this tissue by opening K_{ATP} channels.

Potassium channels are important regulators of resting membrane potential in smooth muscle. In general, these channels are inhibited during agonist-induced contractions [21], producing membrane depolarization which may contribute to extracellular calcium influx via voltage-dependent calcium channels. Conversely, compounds that open these channels tend to relax smooth muscle. It appears that β adrenoreceptor agonists relax smooth muscle in part by augmenting potassium channel activity [22, 23], and compounds that act primarily as potassium channel openers are currently being developed for therapeutic applications. At least three classes of potassium channels are present in airway smooth muscle [21]. Large-conductance, calcium-activated (K_{Ca}) channels are abundant in airway smooth muscle cell membranes and are modulated by agents that affect smooth muscle tone. Delayed rectifier potassium channels are open under resting conditions and may serve to stabilize membrane potential [24]. Although the ATP-sensitive potassium (K_{ATP}) channel has not been characterized fully in airway smooth muscle, there is considerable pharmacological evidence for its presence. The K_{ATP} channel openers cromakalim and levcromakalim hyperpolarize and relax airway smooth muscle [25, 26], effects that can be antagonized by glibenclamide, a blocker of the K_{ATP} channel [27, 28].

We found pharmacological evidence for the presence of both K_{Ca} and K_{ATP} channels in our preparation. Based on the lack of interaction between TEA and a K_{ATP} channel opener in our preparation (fig. 4) and previous work finding little evidence of the effect of TEA (at 1 mmol litre^{-1}) on delayed rectifier channels in airway smooth muscle [20], we assume that TEA acted predominantly on the K_{Ca} channel, although effects on other channel types not yet identified in airway smooth muscle are possible. Block of K_{Ca} channels by TEA increased the sensitivity of the muscle to ACh-induced contraction, consistent with previous studies of smooth muscle [29]. Presumably, K_{Ca} channel block allowed a greater degree of membrane depolarization during block, leading to an increase in calcium influx, intracellular calcium concentration and force. Block of K_{ATP} channels by glibenclamide did not affect ACh-induced contractions, suggesting that this channel is not functionally important during this mode of stimulation in this tissue. However, during precontraction with ACh, this preparation was relaxed readily by the K_{ATP} channel opener YM934, a relaxation that was blocked by glibenclamide, indicating that K_{ATP} channels can modulate functional effects in this tissue.

Previous work has suggested that halothane and other anaesthetics modulate the function of several types of ion channels, including potassium channels. Inhibitory effects of halothane on K_{Ca}-channel function have been demonstrated in several different cell types, including vascular smooth muscle [13], with an ED_{50} of approximately 0.5 mmol litre^{-1} in all studies. Halothane depresses 4-aminopyridine-sensitive potassium currents in coronary arterial smooth muscle cells, suggesting antagonism of delayed rectifier potassium channels [7]. Halothane also depresses the function of a wide variety of both invertebrate and mammalian potassium channels with diverse functional characteristics [15]. In contrast, Franks and Lieb [10] have described a K^+ channel in mollusc neurones that is activated by halothane.

Electrophysiological measurements of the effects of halothane specifically on the K_{ATP} channel have not yet been performed. However, some pharmacological studies have suggested that halothane may activate this channel. Larach and Schuler [12] found that glibenclamide inhibited halothane-induced vasodilatation of coronary resistance vessels in perfused rat hearts. However, this effect was not observed in isolated rings of epicardial coronary vessels denuded of endothelium; glibenclamide actually potentiated the effects of halothane in rings with intact endothelium. Mehr and Lindeman [11] measured the response of peripheral airway resistance, using a wedged bronchoscope technique, to hypocapnia produced by increasing flows of gas free of carbon dioxide in a canine model of asthma (the Basenji–Greyhound dog). They found that the response to hypocapnia was suppressed in dogs anaesthetized with 1.2% halothane, compared with dogs anaesthetized with thiopentone and fentanyl. Pretreatment with glibenclamide aerosolized into the airway via the bronchoscope restored responsiveness to hypocapnia in dogs anaesthetized with halothane, and had no effect in dogs anaesthetized with thiopentone and fentanyl. They concluded that halothane suppressed the response of peripheral airways to hypocapnia by opening K_{ATP} channels.

In contrast with these findings, we found no interaction between the effects of halothane and glibenclamide in canine tracheal smooth muscle. The apparent antagonism by halothane of the ability of YM934, a potassium channel opener, to relax strips precontracted with ACh would suggest that halothane blocks K_{ATP} channels under these conditions. However, it appears that the results of this experiment may be explained primarily by functional antagonism; the effects of YM934 observed in halothane-treated muscles (fig. 6) can be ascribed to the higher ACh concentration necessary to produce an initial force similar to that in control muscles (compare fig. 6 (top and bottom)). Furthermore, there was no evidence of an interaction between the effects of halothane and YM934 on the ACh concentration–response relationship. Direct comparison of our results with the study of Mehr and Lindeman is not possible, because of differences in the breed of dog, location of the airway smooth muscle studied, method used to produce muscle contraction and differences in experimental condition (*in vivo vs in vitro*).

We also studied the interaction of halothane and TEA to determine if any effects of halothane that might have been observed in the glibenclamide procedures were specific to effects on the K_{ATP} channel. Halothane potentiated the effects of TEA on the ACh concentration–response relationship, and TEA potentiated the effect of halothane on muscles precontracted with ACh. Marijic and colleagues [29] observed a similar potentiation of halothane effect by TEA in vascular smooth muscle. The authors suggested, and provided supportive evidence in a subsequent study [7], that halothane antagonized ion fluxes through both potassium and calcium channels. Antagonism of potassium channel function would favour membrane depolarization and increases in muscle tone; antagonism of calcium channel function would decrease intracellular calcium concentration and favour decreases in muscle tone. Under most circumstances, effects on calcium channels predominate, and the muscle relaxes when exposed to halothane. When potassium channels are blocked by TEA, halothane can inhibit only calcium channels, so that its relaxing effect is magnified. Our results are consistent with this explanation. Thus interference with the normal function of ion channels produced by anaesthetics may have opposite effects on physiological function, depending on the experimental conditions.

Acknowledgements

We thank Kathy Street for technical assistance, Janet Beckman and Cathy Nelson for secretarial support, and Yamanouchi Pharmaceuticals for donating the YM934. This study was supported in part by Research Grant HL-45532 from the National Institutes of Health.

References

1. Brichant J-F, Gunst SJ, Warner DO, Rehder K. Halothane, enflurane, and isoflurane depress the peripheral vagal motor

pathway in isolated canine tracheal smooth muscle. *Anesthesiology* 1991; **74**: 325–332.

2. Warner DO, Vettermann J, Brichant J-F, Rehder K. Direct and neurally-mediated effects of halothane on pulmonary resistance *in vivo*. *Anesthesiology* 1990; **72**: 1057–1063.
3. Jones KA, Housmans PR, Warner DO, Lorenz RR, Rehder K. Halothane alters cytosolic calcium transient in tracheal smooth muscle. *American Journal of Physiology* 1993; **265**: L80–L86.
4. Yamakage M. Direct inhibitory mechanisms of halothane on canine tracheal smooth muscle contraction. *Anesthesiology* 1992; **77**: 546–553.
5. Bosnjak ZJ, Supan FD, Rusch NJ. The effects of halothane, enflurane, and isoflurane on calcium current in isolated canine ventricular cells. *Anesthesiology* 1991; **74**: 340–345.
6. Buljubasic N, Flynn NM, Marijic J, Rusch NJ, Kampine JP, Bosnjak ZJ. Effects of isoflurane on K^+ and Ca^{2+} conductance in isolated smooth muscle cells of canine cerebral arteries. *Anesthesia and Analgesia* 1992; **75**: 590–596.
7. Buljubasic N, Rusch NJ, Marijic J, Kampine JP, Bosnjak ZJ. Effects of halothane and isoflurane on calcium and potassium channel currents in canine coronary arterial cells. *Anesthesiology* 1992; **76**: 990–998.
8. MacIver MB, Kendig JJ. Anesthetic effects on resting membrane potential are voltage-dependent and agent-specific. *Anesthesiology* 1991; **74**: 83–88.
9. Korenaga S, Takeda K, Ito Y. Differential effects of halothane on airway nerves and muscle. *Anesthesiology* 1984; **60**: 309–318.
10. Franks NP, Lieb WR. Volatile general anaesthetics activate a novel neuronal K^+ current. *Nature* (*London*) 1988; **333**: 662–664.
11. Mehr EH, Lindeman KS. Effects of halothane, propofol, and thiopental on peripheral airway reactivity. *Anesthesiology* 1993; **79**: 290–298.
12. Larach DR, Schuler HG. Potassium channel blockade and halothane vasodilation in conducting and resistance coronary arteries. *Journal of Pharmacology and Experimental Therapeutics* 1993; **267**: 72–81.
13. Hong Y, Puil E, Mathers DA. Effect of halothane on large-conductance calcium-dependent potassium channels in cerebrovascular smooth muscle cells of the rat. *Anesthesiology* 1994; **81**: 649–656.
14. Pancrazio JJ, Park WK, Lynch C III. Inhalational anesthetic actions on voltage-gated ion currents of bovine adrenal chromaffin cells. *Molecular Pharmacology* 1993; **43**: 783–794.
15. Zorn L, Kulkarni R, Anantharam V, Bayley H, Treistman SN. Halothane acts on many potassium channels, including a minimal potassium channel. *Neuroscience Letters* 1993; **161**: 81–84.
16. Uchida W, Masuda N, Taguchi T, Shibasaki K, Shirai Y, Asano M, Matsumoto Y, Tsuzuki R, Fujikura T, Takenaka T. Pharmacologic profiles of YM934, a novel potassium channel opener. *Journal of Cardiovascular Pharmacology* 1994; **23**: 180–187.
17. Torphy TJ, Hay DWP. Biochemical regulation of airway smooth-muscle tone: an overview. In: Agrawal DK, Townley RG, eds. *Airway Smooth Muscle: Modulation of Receptors and Response*. Boston: CRC Press, 1990; 39–68.
18. Yamamoto K, Morimoto N, Warner DO, Rehder K, Jones KA. Factors influencing the direct actions of volatile anesthetics on airway smooth muscle. *Anesthesiology* 1993; **78**: 1102–1111.
19. Meddings JB, Scott RB, Fick GH. Analysis and comparison of sigmoidal curves: application to dose–response data. *American Journal of Physiology* 1989; **257**: G982–G989.
20. Boyle JP, Tomasic M, Kotlikoff MI. Delayed rectifier potassium channels in canine and porcine airway smooth muscle cells. *Journal of Physiology* (*London*) 1992; **447**: 329–350.
21. Kotlikoff MI. Potassium channels in airway smooth muscle: A tale of two channels. *Pharmacology and Therapeutics* 1993; **58**: 1–12.
22. Kume H, Graziano MP, Kotlikoff MI. Stimulatory and inhibitory regulation of calcium-activated potassium channels by guanine nucleotide-binding proteins. *Proceedings of the National Academy of Sciences USA* 1992; **89**: 11051–11055.
23. Kume H, Takai A, Tokuno H, Tomita T. Regulation of Ca^{2+}-dependent K^+-channel activity in tracheal myocytes by phosphorylation. *Nature* (*London*) 1989; **341**: 152–154.
24. Fleischmann BK, Washabau RJ, Kotlikoff MI. Control of resting membrane potential by delayed rectifier potassium currents in ferret airway smooth muscle cells. *Journal of Physiology* (*London*) 1993; **469**: 625–638.
25. Daniel EE, Jury J. Cromakalim and K^+ channels in canine trachealis. *Pulmonary Pharmacology* 1991; **4**: 209–217.
26. Raeburn D, Brown TJ. RP 49356 and cromakalim relax airway smooth muscle in vitro by opening a sulphonylurea-sensitive K^+ channel: a comparison with nifedipine. *Journal of Pharmacology and Experimental Therapeutics* 1991; **256**: 480–485.
27. Nielsen-Kudsk JE, Bang L, Bronsgaard AM. Glibenclamide blocks the relaxant action of pinacidil and cromakalim in airway smooth muscle. *European Journal of Pharmacology* 1990; **180**: 291–296.
28. Lindeman KS, Fernandes LB, Croxton TL, Hirshman CA. Role of potassium channels in hypoxic relaxation of porcine bronchi in vitro. *American Journal of Physiology* 1994; **266**: L232–L237.
29. Marijic J, Buljubasic N, Coughlan MG, Kampine JP, Bosnjak ZJ. Effect of K^+ channel blockade with tetraethylammonium on anesthetic-induced relaxation in canine cerebral and coronary arteries. *Anesthesiology* 1992; **77**: 948–955.

British Journal of Anaesthesia 1996; **76**: 854–859

Recovery of respiratory ciliary function after depression by inhalation anaesthetic agents: an *in vitro* study using nasal turbinate explants

J. H. RAPHAEL, J. STRUPISH, D. A. SELWYN, H. C. L. HANN AND J. A. LANGTON

Summary

We have developed a human tissue preparation suitable for measurement of cilia beat frequency derived from nasal turbinates. Cilia beat frequency of turbinate explants from 11 patients did not change significantly over a 10-day observation period while maintained in an incubator, with mean cilia beat frequency of 13.1 (SEM 0.3) Hz to 14.4 (0.2) Hz (ANOVA for repeated measures, $P = 0.168$). We have used this preparation to investigate recovery of ciliary function after depression by inhalation anaesthetic agents. Eight or nine turbinate explants were exposed to three times the minimum alveolar concentration (MAC) of halothane, enflurane or isoflurane for a period of 1 h and thereafter to a period of air washout. After exposure to the inhalation agent there was a significant reduction in cilia beat frequency with all three agents: halothane 14.3 (0.4) Hz to 9.5 (0.3) Hz; enflurane 13.7 (0.6) Hz to 10.5 (0.5) Hz; isoflurane 15.9 (0.6) Hz to 10.6 (0.3) Hz. Cilia beat frequency returned to values after air washout that were not significantly different from baseline after 90 min of washout of halothane and 60 min of washout of enflurane and isoflurane (repeated measures ANOVA, unpaired *t* test; $P = 0.01$ at 60 min and $P = 0.31$ at 90 min washout for halothane; $P = 0.83$ at 60 min washout for enflurane; $P = 0.26$ at 60 min washout for isoflurane). (*Br. J. Anaesth.* 1996; **76**: 854–859)

Key words

Anaesthetics volatile, halothane. Anaesthetics volatile, enflurane. Anaesthetics volatile, isoflurane. Lung, trachea.

Mucociliary clearance is an important defence against respiratory tract infections. The depressant effects of inhalation anaesthetic agents on mucus transport *in vivo* are well established in both animals and humans [1, 2], however, the mechanisms involved have not been elucidated. Mucus transport depends on the volume and physical properties of the mucus and on the function of the beating cilia. Cilia beat frequency is an important determinant of mucus transport rate; there is a logarithmic relation between the two such that modest reductions in cilia beat frequency are associated with substantial reductions in mucus transport rate [3, 4].

In a previous study [5] we have demonstrated depression of human respiratory cilia beat frequency with 3 MAC of the three inhalation anaesthetic agents, halothane, enflurane and isoflurane. In this investigation we have studied the duration of cilia beat frequency depression by measuring the recovery characteristics of cilia beat frequency after a period of air washout.

We have developed an alternative source of human respiratory ciliated epithelium suitable for measurement of cilia beat frequency. This is derived from explants of the inferior nasal turbinates removed from patients at elective surgical turbinectomy for a primary diagnosis of tissue hypertrophy. The preparation of these specimens, measurements of cilia beat frequency and the effects of 3 MAC of the inhalation agents followed by a period of air washout are described.

Methods

TISSUE PREPARATION

We collected the inferior nasal turbinates removed from patients at elective surgery with a primary diagnosis of tissue hypertrophy without any history of allergy. The turbinates were rinsed thoroughly in medium 199 (M199) (containing 2.2 g litre^{-1} of $NaHCO_3$ and L-glutamate, GibcoBRL Life Technologies) to remove as much blood and mucus as possible. Discs of the surface ciliated epithelium were removed using a 4-mm biopsy punch (Stiefel Laboratories, Wooburn Green, Bucks, UK). The specimens were rinsed in a mixture made from 100 ml of M199 and 2 ml of antibiotic–antimycotic solution (containing penicillin 10000 u., streptomycin 10 mg, and amphotericin 23 µg ml^{-1}, diluted 1:100; Sigma Chemical Co.). We placed the specimens in 10 ml of culture medium made from 100 ml of medium 199, 10 ml of fetal calf serum (Gibco Life Technologies), 2 ml of antibiotic–antimycotic solution and 1 ml of mixed additives containing insulin 250 µg ml^{-1}, transferrin 250 µg ml^{-1} and hydrocortisone 36 µg ml^{-1}. The specimens were then

---

J. H. RAPHAEL, FRCA, J. STRUPISH, BSC, D. A. SELWYN, FRCA, H. C. L. HANN, BSC, J. A. LANGTON*, MD, FRCA, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. Accepted for publication: January 23, 1996.

*Current address: Department of Anaesthesia, Derriford Hospital, Plymouth.

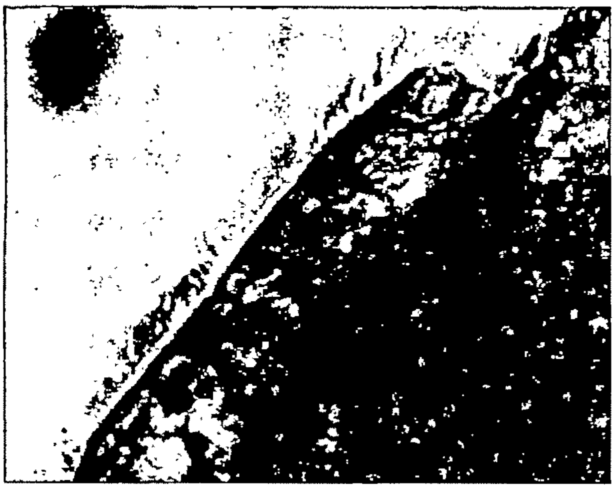


Figure 1 Photograph of ciliated edge of nasal turbinate explant.

incubated at 37 °C with occasional mixing for 1 h to separate the mucus. We then transferred the specimens into multidishes with 3 ml of culture medium per well and incubated at 37 °C in 5% carbon dioxide–air. The medium was changed after 24 h and every 3–4 days thereafter.

MEASUREMENT OF CILIA BEAT FREQUENCY

Cilia beat frequency was measured using a modification of the transmitted light technique that we have described previously [6]. The 4-mm disc of tissue was placed in a purpose-built perfusion chamber system and images of the ciliated epithelium were produced using a Nikon microscope by viewing the edge of the disc (fig. 1). The chamber consists of an aluminium block with integral channels at two sides and reversibly sealed coverslips at the top and bottom. The chamber has a depth of 0.85 mm and an internal volume of 1.1 ml. The chamber is perfused using connecting tubing passing from a bottle of Hanks buffered salt solution (HBSS) into the entry port of the chamber and out from its exit port through connecting tubing into a collecting beaker.

HBSS flows from a container immersed in a water bath maintained at 37 °C under the effect of gravity at a flow rate of 0.5 ml min^{-1} measured by a calibrated photoelectric drop counter. Air flows into the container at 1000 ml min^{-1}. The perfusion chamber is maintained at 37 ($\pm$0.1) °C using a thermostatically controlled heating element mounted on the underside of the chamber.

Images of the ciliated epithelium were produced using differential interference contrast microscopy (Nikon Diaphot 200, Nikon UK). Using a 60 × objective with a 10 × ocular lens, the image obtained from the microscope was transmitted via a video camera (Panasonic vw-CL 110-AE) to a high resolution video monitor (Sony KX-14CPI). A low pass filtered pinhead photodiode with a cut-off above 25 Hz was attached to the monitor screen and the image of the sample moved so that the cilia interfered with the light reaching the photodiode. The magnification of the optical system and aperture of the photodiode results in 3–5 cilia being captured by the photodiode and as adjacent cilia beat in phase, the frequency of interruption to the light reaching the photodiode by this number of cilia is representative of cilia beat frequency.

The output was transferred to a Gould 20-MHz cathode ray oscilloscope to confirm the detection of ciliary movements. Voltage changes across the photodiode were passed simultaneously via an analogue-to-digital converter to a computer (Dell 386sx) that samples voltage at a frequency of 200 Hz. The voltage signals were collected over a period of 15 s by recording continuously from one edge. These data were then divided into three sequential 5-s intervals for analysis.

The data were transferred to an RM Centra V466 computer and analysed by software in Mathematica 2.2 to provide a power spectrum using fast Fourier transforms. Mean frequencies less than 2 Hz were filtered out to eliminate artefacts of low frequency caused by sudden movements of the light pen or microscope stage. The peak of the power spectrum was taken to represent cilia beat frequency. The whole apparatus is mounted on a concrete block to reduce extraneous vibrations that interfere with photometric techniques of measurement. Acceptable ciliated edges for measurement were deemed to be those devoid of mucus, and at least 60 μm long.

STATISTICAL ANALYSIS

The mean of peak cilia beat frequencies from the power spectrum was computed for each sample at each time point. The data were analysed by analysis of variance for repeated measures. If this was significant the data were analysed by unpaired *t* tests with Bonferroni correction, comparing baseline cilia beat frequency with that measured at subsequent times. Significance was taken as $P < 0.05$.

Turbinate cilia survival characteristics

In order to investigate the survival characteristics of cilia from the turbinate preparations over time, we measured cilia beat frequency of samples obtained from 11 patients. These patients had a mean age of 28.3 (range 21–56) yr, all were non-smokers, receiving no regular medications, who were anaesthetized with propofol for induction of anaesthesia, morphine or fentanyl for analgesia, and isoflurane for maintenance of anaesthesia. All patients received cocaine 200 mg and adrenaline 1 mg applied topically to the nasal cavity before surgical excision.

We measured cilia survival characteristics over a period of 10 days from discs obtained from the 11 patients by measuring cilia beat frequency 1, 3, 6, 8 and 10 days after surgical excision. On each of these days we transferred six discs from any six of the patients into the perfusion chamber and measured cilia beat frequency 1–2 h after removal from the incubator. After measurement, these discs were discarded and on subsequent days this process was repeated with another set of discs from any six of the 11 patients stored in the incubator. Between six and 10 readings of cilia beat frequency were obtained from each disc.

Effect of 3 MAC of the inhalation agents and a period of air washout

Samples of human respiratory ciliated epithelium were obtained in the same manner as above from the inferior nasal turbinates of nine patients undergoing turbinectomy surgery for a primary diagnosis of turbinate hypertrophy. The patients were aged 30.1 (range 18–43) yr, seven were male, and all were healthy, non-smokers.

Discs of 4 mm from the patient's turbinates of variable storage period and up to 6 days old were mounted in the perfusion chamber. The chamber was perfused from a delivery bottle of HBSS under the effect of gravity at 0.5 ml min^{-1}. Air at 1000 ml min^{-1} was passed through a Tec 3 vaporizer before passing into the delivery bottle. The vaporizer was set at a concentration of 3 MAC for unpremedicated young adults at 37 °C; this represented 2.25 % for halothane, 5 % for enflurane and 3.6 % for isoflurane. We have shown previously that this apparatus delivers the volatile anaesthetic agents into the perfusate and equilibrates within 15 min [5]. Samples from eight patients were exposed to halothane and isoflurane and samples from nine patients to enflurane. After exposure to 3 MAC of one of the three inhalation agents for a period of 1 h, we recorded 6–10 readings of ciliary beat frequency. We then exposed the samples to air alone by perfusing them from a separate delivery bottle of HBSS and measured cilia beat frequency after exposure to air at 30-min intervals for 1.5 h.

Results

Cilia beat frequency of the turbinate samples did not change significantly over the 10-day observation period while maintained in the incubator, with mean cilia beat frequency ranging from a minimum of 13.1 (SEM 0.3) Hz to a maximum of 14.4 (0.2) Hz (MANOVA for repeated measures, $P = 0.168$) (table 1).

Turbinate explants from eight patients were exposed to 3 MAC of halothane and subsequently to air. Mean cilia beat frequency after exposure to halothane for 1 h was 9.5 (SEM 0.32) Hz, after 30 min of air washout 8.3 (0.50) Hz, after 1 h of air washout 12.6 (0.5) Hz and after 90 min of washout 13.7 (0.4) Hz. These compared with a pretreatment value of 14.3 (0.4) Hz. After 1 h of air washout, cilia beat frequency remained significantly depressed, but after 90 min of air washout it had returned to a value that was not significantly different from the pretreatment value (repeated measures ANOVA, unpaired, *t* test with Bonferroni correction, $P = 0.01$ at 1 h and $P = 0.31$ at 1.5 h of air washout compared with pretreatment control) (fig. 2).

Table 1 Cilia beat frequency (CBF) of turbinate explants over 10 days (mean (SEM))

Day	CBF (Hz)	Ciliated edges measured
1	14.0 (0.33)	109
3	14.5 (0.24)	99
5	13.8 (0.26)	123
8	13.1 (0.24)	112
10	13.2 (0.28)	97

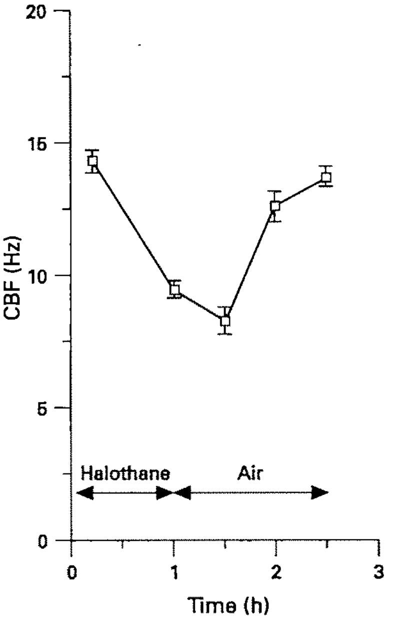


Figure 2 Cilia beat frequency (CBF) after 3 MAC of halothane for 1 h and air washout for 1.5 h (mean, SEM).

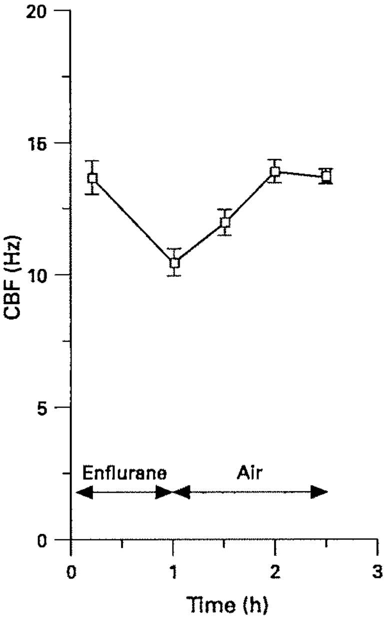


Figure 3 Cilia beat frequency (CBF) after 3 MAC of enflurane for 1 h and air washout for 1.5 h (mean, SEM).

Mean cilia beat frequency after exposure to enflurane for 1 h was 10.5 (0.51) Hz, after 30 min of air washout 12.0 (0.4) Hz and after 1 h of air washout 13.9 (0.4) Hz compared with a treatment value of 13.7 (0.6) Hz. Mean cilia beat frequency had returned to values that were not significantly different from pretreatment values after an air washout period of 1 h (repeated measures ANOVA, unpaired *t* test with Bonferroni correction, $P = 0.83$, at 1 h of air washout compared with pretreatment controls) (fig. 3).

Mean cilia beat frequency after exposure to isoflurane for 1 h was 10.6 (0.30) Hz and after 1 h of

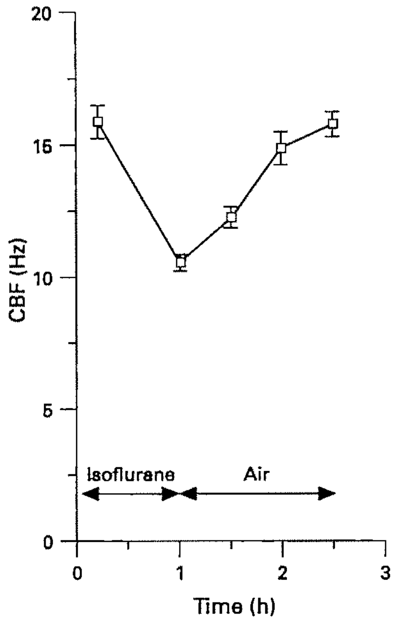


Figure 4 Cilia beat frequency (CBF) after 3 MAC of isoflurane for 1 h and air washout for 1.5 h (mean, SEM).

air washout 14.9 (0.6) Hz compared with a pretreatment value of 15.9 (0.6) Hz. Mean cilia beat frequency had returned to values that were not significantly different from pretreatment values after an air washout period of 1 h (repeated measures ANOVA, unpaired t test with Bonferroni correction, $P = 0.26$ at 1 h of air washout compared with pretreatment controls) (fig. 4).

Discussion

Cilia beat frequency of the nasal turbinate explants was unchanged during storage in a controlled environment for up to 10 days. Using this preparation there was reversible depression of cilia beat frequency *in vitro* after exposure to 3 MAC of the three inhalation agents halothane, enflurane or isoflurane; however the reduction was more prolonged after exposure to halothane compared with the two other agents.

Almost all human *in vitro* studies of respiratory ciliary function have used cytological specimens from brushings of the respiratory tract [7]. Nasal brushings are favoured because this is less invasive and cilia beat frequency is similar to bronchial ciliated specimens [8] implying nasal cilia are representative of cilia further down the respiratory tract. However, such exfoliated tissue samples may present problems as the cells are disrupted from their basement membrane, they are prone to sample movement which interferes with measurement of cilia beat frequency [9] and we have found that the samples are suitable for analysis only on the day of removal, which causes logistical restraints.

We intended originally to culture the ciliated cells from excised nasal turbinates using techniques described by Devalia and colleagues [10]; however, we noticed that the cilia of the turbinate explants remained functional for more than 1 week, despite no evidence of growth, and therefore explored the use of these preparations. We continued to use the growth factors for tissue storage as described in the earlier study [10], although this may not in fact be necessary.

Historically, *in vitro* samples of respiratory ciliated epithelium were provided by biopsy of the inferior nasal turbinates and used to diagnose such conditions as cystic fibrosis; however, such techniques became unpopular because they were performed under local anaesthesia with its attendant ciliotoxic effects and there was a risk of haemorrhage associated with this procedure. We considered that biopsies obtained from the inferior nasal turbinates had advantages over nasal brushings. Such preparations may provide a better model of *in vivo* ciliary behaviour as much of the adjacent tissue is retained and the use of larger samples reduces the likelihood of sample movement which interferes with measurement of cilia beat frequency. Furthermore, we had found that cilia of turbinate explants remained beating for up to 10 days after excision and could provide a tissue source in the laboratory. In addition, the specimens derived from the turbinates were found to have superior edges from which to measure cilia beat frequency. Using explants from excised turbinates overcomes the problems of haemorrhage from turbinate biopsies referred to earlier and the ability to store the tissue for use more than 24 h after excision overcomes the short-lived effects of topical vasoconstrictors and local anaesthetics on ciliary function [11].

Clearly such samples are derived from patients with abnormal turbinates requiring surgical excision and the possibility that their cilia may be abnormal was considered. We therefore only used tissue from turbinates removed from patients with a diagnosis of tissue hypertrophy causing nasal obstruction without any history of allergy. Other workers have demonstrated that the mucus transport rate of such turbinates is normal, implying normal mucociliary function [11].

Cilia beat frequency of explants was within the range reported by previous workers using different ciliated preparations and different measurement techniques of 11–18 Hz [9]. The range of ciliary beat frequencies we computed from the nasal brushings of 11.2–12 Hz [6] was lower than that measured from the turbinate explants of 11.6–15.0 Hz. This difference represents different patterns of interference with the light beam, the rate of which is deemed to represent ciliary beat frequency. The diameter of the light pen images 3–5 cilia in any plane and cilia throughout the depth of the field. Because adjacent cilia are co-ordinated and beat in synchrony, interference in the light path by multiple cilia imaged with each position of the light pen provides a measure of cilia beat frequency. The depth and co-ordination of adjacent cilia may well be different in cytological specimens compared with explants. With turbinate explants there is a greater depth of ciliated tissue interfering with the light path but the greater ciliary continuity may provide better co-ordination. These factors may explain the different cilia beat frequency computed. Nevertheless, for each specimen, whether nasal brushings or turbinate explants, cilia beat frequency was within the range found by other workers, was reproducible and predictably responsive to pharmacological agents.

There are few previous studies of the effects of inhalation anaesthetic agents on cilia beat frequency with which to compare this investigation; however, other studies found similar reductions in cilia beat frequency. Using rabbit trachea, Lee and Park found reductions in cilia beat frequency with 3 MAC of halothane of 22 %. This compares with our reductions at these concentrations of 25 %. In the case of enflurane, these workers found reductions in cilia beat frequency at 3 MAC of 26 % which compares with our finding of 26 % [12]. Depression of cilia beat frequency in our turbinate preparations of 33 %, 25 % and 33 % with halothane, enflurane and isoflurane, respectively, differs from that found at 1 h with nasal brushings in our previous study [5], where we found reductions of 28 %, 10 % and 2 % with these three agents. The difference is because of the use of a different tissue preparation and interestingly the results with the turbinate preparations are closer to those found by Lee and Park using rabbit trachea than our measurements from nasal brushings. The turbinate samples may be a more physiological tissue than exfoliated cells to investigate ciliary function.

Cilia beat frequency is an important determinant of mucus transport rate. Forty years ago, Hill investigated the movement of carborundum particles across frog oesophagus and rat trachea [13]. She described a hyperbolic relationship between mucus transport rate and particle velocity such that there were disproportionately larger decreases in mucus transport rates at lower particle velocities. It was hypothesized that this relationship arose because the transfer of power from the beating cilia to the mucus was most effective within a narrow range of cilia beat frequencies.

Puchelle and Zahm studied the relationship between the transport rate of sputum from bronchitic patients across mucus-depleted frog palate and the rheological properties of sputum [14]. Not surprisingly, the rheological properties of increased viscosity, increased elasticity and reduced spinnability were associated with reduced transport rates; however the most important determinant of mucus transport rate found by step-by-step multiple regression was ciliary beat frequency.

Duchateau and colleagues investigated the relationship between nasal cilia beat frequency measured photometrically from biopsies *in vitro* with nasal mucociliary clearance of dye and saccharin *in vivo* in 31 healthy volunteers [3]. A good correlation was found between the logarithm of mucus clearance rate and cilia beat frequency.

Hee and Guillerm similarly described a non-linear relationship between cilia beat frequency and mucus transport rates in sheep such that modest reductions in cilia beat frequency were associated with large reductions in mucus transport rates [4]. These studies suggest that cilia beat frequency has an important role in determining the transport rate of mucus.

The return to baseline values of cilia beat frequency after exposure to 3 MAC of halothane, enflurane and isoflurane for 1 h took 1 h for enflurane and isoflurane and 1.5 h for halothane. Interestingly, cilia beat frequency measured 30 min after ceasing exposure to the inhalation agent demonstrated some recovery with enflurane and isoflurane but a further reduction with halothane.

Differences in recovery time and effects of early washout with the three agents may be related to their different recovery characteristics from general anaesthesia which is dependent on their physical properties. Halothane has a greater lipid–water solubility coefficient than the two other agents and may take longer to diffuse out from the fat soluble tissues of the preparation. The mechanism of continuing reduction in cilia beat frequency after cessation of halothane is unknown but is an interesting finding that merits further investigation. The only comparable work is by Gyi, O'Callaghan and Langton investigating the effects of halothane alone on cilia beat frequency. Their data failed to show a reversal of effect after air washout for 50 min [15]. This concurs with our findings at 1 h.

There are no data available comparing the duration of reduction in mucus transport or clinical data comparing the incidence of infective respiratory problems with different inhalation agents.

The time for reversal of depression in ciliary function found in this study may appear to be clinically insignificant, especially in the light of the longer duration of depression of mucus transport rates demonstrated with inhalation anaesthetics *in vivo*. Forbes and Gamsu measured tantalum bronchographic clearance in dogs anaesthetized with halothane and found that 1.2 MAC of halothane administered for 2 h delayed the clearance of tantalum for more than 4 h after termination of anaesthesia [1]. This may represent additional effects of the anaesthetics on the mucus itself. Alternatively, even relatively short periods of depression of ciliary beat frequency which produce mucus stasis could alter the physical properties of mucus and therefore impair mucus transport for a longer period.

References

1. Forbes AR, Gamsu G. Mucociliary clearance in the canine lung during and after general anesthesia. *Anesthesiology* 1979; **50**: 26–29.
2. Lichtiger M, Landa JF, Hirsch JA. Velocity of tracheal mucus in anesthetized women undergoing gynecologic surgery. *Anesthesiology* 1975; **42**: 753–755.
3. Duchateau GS, Graamans K, Zuidema J, Merkins FW. Correlation between nasal ciliary beat frequency and mucus transport rate in volunteers. *Laryngoscope* 1985; **95**: 854–859.
4. Hee J, Guillerm R. Discussion on smoke and mucociliary transport. *European Journal of Respiratory Diseases* 1985; **66** (Suppl. 139): 86–88.
5. Raphael JH, Selwyn DA, Mottram SD, Langton JA, O'Callaghan C. Effects of 3 MAC of halothane, enflurane and isoflurane on human nasal cilia beat frequency *in vitro*. *British Journal of Anaesthesia* 1996; **76**: 116–121.
6. Selwyn DA, Gyi A, Raphael JH, Key A, Langton JA. A perfusion system for the *in vitro* measurement of cilia beat frequency. *British Journal of Anaesthesia* 1996; **76**: 111–115.
7. Rutland J, Cole PJ. Non-invasive sampling of nasal cilia for measurement of beat frequency and study of ultrastructure. *Lancet* 1980; **2**: 564–565.

8. Low PP, Luk CK, Dulfano MJ, Finch PJP. Ciliary beat frequency of human respiratory tract by different sampling techniques. *American Review of Respiratory Disease* 1984; **130**: 497–498.
9. Yager J, Chen T-M, Dulfano MJ. Measurement of frequency of ciliary beats of human respiratory epithelium. *Chest* 1978; **73**: 627–633.
10. Devalia JL, Sapsford RJ, Rusznak C, Toumbis MJ, Davies RJ. The effects of salmeterol and salbutamol on ciliary beat frequency of cultured human bronchial epithelial cells, in vitro. *Pulmonary Pharmacology* 1992; **5**: 257–263.
11. Mason JDT, Aspden TJ, Adler J, Jones NS, Illum L, Davis SS. Measurement of nasal mucociliary transport rates on the isolated human inferior turbinate. *Clinical Otolaryngology* 1995; **20**: 530–535.
12. Lee KS, Park SS. Effect of halothane, enflurane and nitrous oxide on tracheal ciliary activity *in vitro*. *Anesthesia and Analgesia* 1980; **59**: 426–430.
13. Hill JR. The influence of drugs on ciliary activity. *Journal of Physiology (London)* 1957; **139**: 157–166.
14. Puchelle E, Zahm JM. Influence of rheological properties of human bronchial secretions on the ciliary beat frequency. *Biorheology* 1984; **21**: 265–272.
15. Gyi A, O'Callaghan C, Langton JA. Effect of halothane on cilia beat frequency of ciliated human respiratory epithelium *in vitro*. *British Journal of Anaesthesia* 1994; **73**: 507–510.

British Journal of Anaesthesia 1996; **76**: 860–867

Effect of halothane on myocardial reoxygenation injury in the isolated rat heart

W. SCHLACK, M. HOLLMANN, J. STUNNECK AND V. THÄMER

Summary

Several studies have reported a protective effect of halothane on myocardial injury in an ischaemia–reperfusion situation. It is unclear if the protection is a result of the haemodynamic effects of halothane or if halothane has a specific action on ischaemia or reperfusion pathomechanisms. To examine this question, we have used an isolated rat heart model where heart rate (300 beat min^{-1}), ventricular volume and coronary flow are constant. Left ventricular developed pressure (LVDP) and release of creatine kinase (CK) were measured as variables of myocardial performance and cellular injury, respectively. Five control hearts were subjected to 35 min of low-flow (2 ml min^{-1}) anoxic and substrate-free perfusion and were then perfused for 1 h with the oxygenated buffer. In the treatment groups, halothane 0.4 mmol $litre^{-1}$ was added during the first 30 min of anoxic perfusion ($n = 5$) or during the first 30 min of reoxygenation ($n = 5$). In five additional hearts, the effect of halothane 0.4 mmol $litre^{-1}$ was tested under normoxic conditions. Mean basal CK release was 0.29 (SEM 0.13) iu g^{-1} min^{-1} and LVDP was 105.5 (4.0) mm Hg. Under normoxic conditions, halothane reduced LVDP to 52.0 (2.6) mm Hg. In control hearts, the major cell injury occurred at the onset of reoxygenation (CK release increased to 149.1 (9.1) iu g^{-1} min^{-1}) and functional recovery after 1 h of reoxygenation was poor (control LVDP, 14.2(2.)% of baseline). Halothane during anoxia attenuated myocardial injury only moderately (CK release 50.2(5.7) iu g^{-1} min^{-1}) and LVDP recovered to 30.8(3.0)% (each $P < 0.05$ *vs* control). When halothane was administered at reoxygenation, CK release was reduced to 10.1(0.9) iu g^{-1} min^{-1} and LVDP recovered to 69.4(4.9)% (each $P < .05$ *vs* control). We conclude that halothane not only attenuated ischaemic injury but had a specific protective action against reoxygenation injury. (*Br. J. Anaesth.* 1996; **76**: 860–867).

Key words

Anaesthetics volatile, halothane. Heart, ischaemia. Heart, myocardial injury. Heart, isolated preparation. Model, heart. Rat.

Reperfusion of temporarily ischaemic myocardium can initiate cellular and biochemical changes which reduce the amount of potentially salvageable myocardium ("reperfusion injury"). The term "lethal reperfusion injury" is used for the irreversible deterioration of myocardium that can be reduced by modifications of the conditions of reperfusion [1]. Some experimental evidence suggests that halothane may have myocardial protective properties in an ischaemia–reperfusion situation. Halothane anaesthesia reduced infarct size in a rabbit model with coronary occlusion and subsequent reperfusion, compared with i.v. anaesthesia with propofol, pentobarbitone or ketamine [2]. The results in non-reperfusion infarct models are contradictory; in a dog model, a reduction in infarct size was reported compared with awake controls [3], while an increase in infarct size was found in rats [4]; both studies explained their findings by the haemodynamic effects of halothane. In a pig model (with collateral circulation after a stenosis operation at a young age), halothane had no effect on infarct size [5].

Administration of halothane during hypoperfusion (low coronary perfusion pressure) to isolated guinea pig hearts, reduced the loss of adenosine and inosine during early reperfusion [6] and improved functional recovery [7]. When supplied to isolated working rat hearts before or during cardioplegic arrest, halothane did not cause preservation of ATP during the ischaemic period, but led to an improved recovery of ATP content and myocardial function during the following reperfusion period [8]. In the same model, lower calcium accumulation during cardioplegic arrest and reperfusion, and better recovery of microscopic signs of ischaemic cell damage were found when halothane was added to the perfusion medium (before and after ischaemia). Similarly, administration of halothane during hypoxic perfusion, and for the first 10 min of reoxygenation, resulted in better recovery of contractile function in isolated guinea pig hearts [9].

While most of the above studies found evidence for the cardioprotective effects of halothane, it is unclear if this protection is caused by the haemodynamic effects of halothane (i.e. a reduction in sympathetic tone, myocardial inotropy and myocardial work) or if halothane has specific protective

---

WOLFGANG SCHLACK*, MD (Institut für Klinische Anaesthesiologie); MARKUS HOLLMAN, CAND MED, JÖRG STUNNECK, CAND MED, VOLKER THÄMER, MD (Physiologisches Institut I); Heinrich-Heine-Universität, Düsseldorf, Germany. Accepted for publication: January 12, 1996.

Correspondence to W. S.

effects against ischaemia or reperfusion pathomechanisms. In addition, it is not possible to distinguish from these studies if the protective effects occur before, during or after the ischaemic period.

To examine these questions, we have used an isolated rat heart model so that extrinsic humoral and autonomic nervous system influences could be excluded and ventricular volume, coronary flow and heart rate could be kept constant. In order to differentiate between anti-ischaemic and protective effects against reperfusion injury, halothane was supplied to the myocardium only during a state of oxygen and substrate deprivation (simulated ischaemia) or only during the initial period, when oxygen and substrates were re-supplied (simulated reperfusion).

Materials and methods

The study was performed in accordance with the regulations of the German Animal Protection Law and local institutional regulations.

EXPERIMENTAL PREPARATION

We excised hearts from 200–250-g male Wistar rats, anaesthetized with halothane, and mounted them on a Langendorff perfusion system. Retrograde perfusion was initiated with an oxygenated modified Krebs–Henseleit buffer containing (mmol litre^{-1}): NaCl 116, KCl 4.7, $MgSO_4$ 1.1, KH_2PO_4 1.17, $NaHCO_3$ 24.9, $CaCl_2$ 2.52, glucose 8.3 and pyruvate 2.0, and was gassed with 95% oxygen–5% carbon dioxide. Flow in the system was controlled by two calibrated roller pumps (Model 7518, Cole-Parmer Instruments, IL, USA). After ligating both venae cavae, the right ventricle was vented via the pulmonary artery with a Teflon catheter (1.2-mm outer diameter). Heart rate was maintained at 300 beat mean^{-1} by atrial pacing. The stimulation voltage was maintained at 20% above threshold (control 2–4 V) and was adjusted continuously throughout the experiment (up to 12 V in reperfused hearts, if necessary). After completion of the experimental preparation, the heart was placed in a water-jacketed chamber at 37 °C, filled with humidified, warmed air. During surgical preparation, hearts were perfused at a flow rate of 15 ml min^{-1}. Coronary flow rate was adjusted in order to achieve a coronary perfusion pressure (measured by P23 ID, Statham) of 100 mm Hg and was then kept constant throughout the normoxic perfusion period.

The buffer for anoxic and substrate-free perfusion contained (mmol litre^{-1}): NaCl 126.3, KCl 4.7, $MgSO_4$ 1.1, KH_2PO_4 1.17, $NaHCO_3$ 24.9, $CaCl_2$ 2.52, and was gassed with 95% nitrogen–5% carbon dioxide. During anoxic perfusion, the heart chamber was filled with a humidified, warmed 95% nitrogen–5% carbon dioxide mixture.

A saturated solution of halothane was prepared in anoxic buffer and infused into the perfusion system near the aortic cannula at appropriate fractions of total coronary flow in order to achieve a final concentration of 0.4 mmol litre^{-1} using a calibrated syringe pump (Model 5003, Precidior Infors, Basel, Switzerland). Only glass or Teflon tubing was in contract with the halothane-containing perfusion medium. Halothane concentrations were determined in the saturated solution by gas chromatography.

HAEMODYNAMIC MEASUREMENTS

For measurements of left ventricular pressure, a latex balloon (size No. 5, Hugo Sachs Elektronik, March, Germany) was introduced into the left ventricle via the cut mitral valve. The balloon was fixed at the tip of a stainless steel cannula (length 5.9 cm) which was connected directly to a pressure transducer (Gould P23, Cleveland, OH, USA). Left ventricular pressure and, by electronic differentiation, dP/dt, were monitored continuously on an ink recorder (Gould, Mark 260, Cleveland, OH, USA). At the beginning of each experiment, the latex balloon was filled, air-bubble free, with normal saline to achieve an end-diastolic left ventricular pressure of 5 mm Hg. This volume was then held constant for the remainder of the experiment. Left ventricular pressure and coronary perfusion pressure signals were digitized at a sampling rate of 2000 Hz using an analogue-to-digital converter (Data Translation 2801, Marlboro, MA, USA) and then processed further on a personal computer system. Left ventricular end-diastole was determined as the point when left ventricular dP/dt started its rapid upstroke after crossing the zero line. Left ventricular end-systole was defined as the point of minimum dP/dt [10]. Left ventricular peak systolic pressure (LVSP), end-diastolic pressure (LVEDP), developed pressure (LVDP), and maximum and minimum dP/dt (dP/dtmax and dP/dtmin) were obtained from the digitized signals. Only hearts with an LVSP greater than 95 mm Hg during the initial control period were used for the study.

METABOLIC MEASUREMENTS

Aliquots from the perfusion medium and the coronary venous effluent perfusate were sampled anaerobically at the times indicated. Samples were processed immediately for P_{O_2} measurements (ABL 30, Radiometer, Copenhagen, Denmark). Oxygen consumption ($\dot{V}_{O_2}$) was calculated according to Fick's principle with the use of Bunsen's absorption coefficient ($\alpha' = 0.036$ µl × mm Hg^{-1} × ml^{-1}) at 37 °C as follows:

$$\dot{V}_{O_2}(\mu l\ min^{-1}) = (Pa_{O_2} - Pv_{O_2})\,\alpha'\,CF$$

where Pa_{O_2} = arterial P_{O_2}, Pv_{O_2} = venous P_{O_2} (both in mm Hg) and CF = coronary flow (ml min^{-1}).

For determination of creatine kinase (CK) release, 1-min samples of the effluent were collected at the times indicated (fig. 3). CK activity was measured with an "optimized standard method" according to the recommendations of the Deutsche Gesellschaft für Klinische Chemie (CK test, Boehringer, Mannheim, Germany). After each experiment, the dry weight of the hearts was measured. Myocardial oxygen consumption and creatine kinase release were expressed per gram of dry tissue.

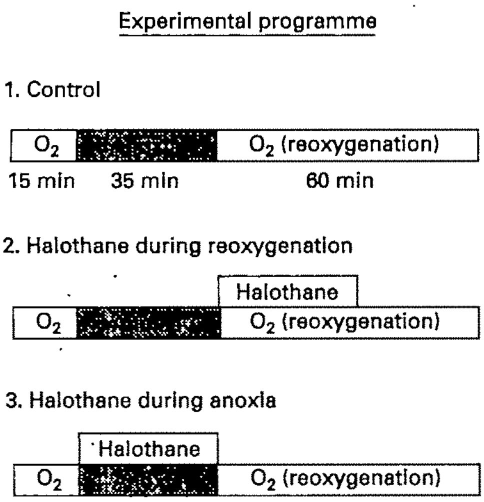


Figure 1 Experimental programme.

EXPERIMENTAL PROGRAMME

After mounting the heart on the Langendorff apparatus, a preparation and stabilization period of 30 min was allowed. The experimental programme consisted of three experimental phases: baseline, anoxia and reoxygenation (fig. 1). After a 15-min baseline period with two control measurements of all experimental variables, the hearts underwent 35 min of anoxic and substrate-free perfusion at a coronary flow of 2 ml min^{-1}. After the anoxic period, the hearts were re-supplied with oxygen, glucose and pyruvate by changing back to the initial normoxic perfusion conditions for 1 h (reoxygenation). Halothane was added to the perfusion medium to achieve a concentration of 0.4 mmol $litre^{-1}$ during the first 30 min of anoxic perfusion (halothane–anoxia, $n = 5$) or during the first 30 min of reoxygenation starting with a 1-min wash-in of the substance (halothane–reoxygenation, $n = 5$). Five hearts served as controls and underwent the anoxia–reoxygenation programme without receiving halothane. Five hearts received halothane 0.4 mmol $litre^{-1}$ for 15 min during normoxic perfusion conditions for assessment of the haemodynamic effects of halothane on normal myocardium in this experimental model.

DATA ANALYSIS

Data are presented as mean (SEM). The effects of halothane on normal myocardium were assessed by Student's *t* test for paired observations. In the anoxia–reoxygenation experiments, statistical analysis was performed by two-way analysis of variance (ANOVA) for time and treatment (experimental group) effects. If an overall significant difference between groups was found, comparison was made for each time using one-way ANOVA followed by the Tukey–Kramer post-test when appropriate.

Results

A total of 28 hearts were used. Eight did not fulfil the predefined quality criteria (LVDP > 95 mm Hg at a coronary perfusion pressure of 100 mm Hg) and were excluded from the study. Mean dry heart weight was 0.168 g (range 0.15–0.18 g).

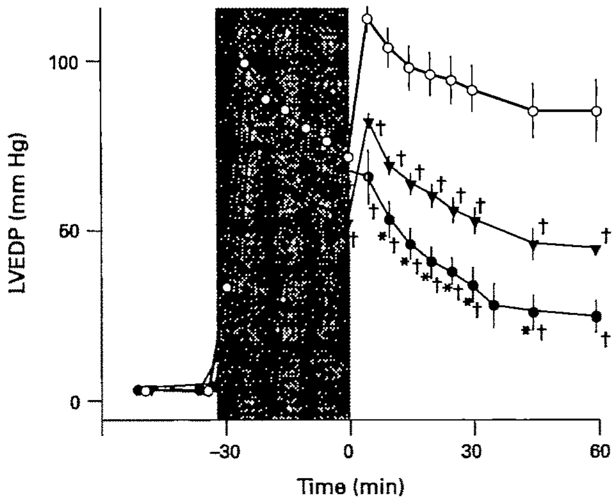


Figure 2 Effect of halothane 0.4 mmol $litre^{-1}$, given during the first 30 min of anoxic perfusion (▼) or during the first 30 min of reoxygenation (●), on left ventricular end-diastolic pressure (LVEDP) as a variable of myocardial contracture (mean, SEM). †$P < 0.05$ *vs* control hearts; *$P < 0.05$ halothane–anoxia *vs* halothane–reoxygenation. Note that in control hearts (○) contracture developed with the onset of reoxygenation. This phenomenon was absent when halothane was given during reoxygenation, but persisted when halothane was given during anoxia.

HAEMODYNAMIC FUNCTION

Basal values and effect of halothane on normal myocardium

In five additional hearts, we investigated the effects of halothane 0.4 mmol $litre^{-1}$ on normal myocardium (measurements were made after 15 min under steady state conditions). Halothane reduced LVDP from 99.2 (1.8) to 52.0 (2.6) mm Hg ($P < 0.001$). LVEDP was 4.0 (0.3) mm Hg before and 2.9 (0.4) mm Hg after administration of halothane ($P < 0.05$). $\dot{V}O_2$ decreased from 869.6 (29.5) to 681.0 (21.0) µl min^{-1} g^{-1} ($P < 0.001$). After discontinuation of halothane, recovery to baseline values occurred within 5 min.

Anoxic contracture development

During anoxic perfusion, a progressive increase in LVEDP was noted in all groups (fig. 2). the time of onset of anoxic contracture was defined as the time at which the end-diastolic pressure had increased by 2 mm Hg; it was similar in all three groups (control 140 (17) s; halothane–anoxia 133 (18) s; halothane–reperfusion 150 (10) s). The maximum level of contracture was reached within 10 min (ns between groups) and LVEDP decreased gradually during the anoxic period. The level of contracture was reduced in the halothane–anoxia group; at the end of the anoxic period, LVEDP was 55.2 (2.0) mm Hg compared with 71.2 (5.1) mm Hg in control hearts ($P < 0.05$) and 69.2 (4.3) mm Hg in hearts treated during reperfusion ($P < 0.05$).

End-diastolic pressure after reoxygenation

The main effect on functional recovery during reoxygenation was a difference in the behaviour of end-diastolic pressure of the experimental groups (fig. 2). In the control group, there was an increase in LVEDP by a mean of 40.0 mm Hg with the onset of reoxygenation (reoxygenation-induced contracture), followed by a slow decrease in LVEDP during the rest of the reoxygenation period to 85.3 mm Hg at 60 min of reoxygenation. The hearts treated with halothane during anoxia had a lower LVEDP before the onset of reoxygenation (51.8 mm Hg) than the two other groups, but then also showed reoxygenation-induced contracture (by 30.0 mm Hg). LVEDP was, however, lower compared with untreated hearts and showed a faster recovery to 43.9 mm Hg at 60 min of reoxygenation. In the group treated with halothane at reoxygenation, reoxygenation-induced contracture was absent and LVEDP decreased rapidly, reaching 24.2 mm Hg at 60 min of reoxygenation.

Recovery of contractile function during reoxygenation

LVDP was similar in all groups (about 105 mm Hg) during baseline measurements before anoxia and then declined rapidly to 0 mm Hg during anoxic perfusion (fig. 3, top). In control hearts, recovery of LVDP started at 30–40 min of reoxygenation and reached 15.4 % of baseline values after 60 min. In hearts treated with halothane during anoxia, recovery was better, starting at 20–30 min of reoxygenation and reaching 32.4 % of baseline values. The best functional recovery was seen in hearts treated with halothane only during reoxygenation; recovery started within the first 5 min and reached 70.4 % of baseline at 60 min of reoxygenation. After discontinuation of halothane at 30 min of reoxygenation, LVDP showed a steep increase by a mean of 32 mm Hg within the next 5 min.

LVSP (table 1) in this experimental model can be regarded as the sum of LVEDP and LVDP. Consequently, it showed a different behaviour between the three groups. In control hearts, LVSP remained almost unchanged during the course of the experiment. In hearts treated with halothane during anoxia, LVSP was reduced compared with baseline values at the onset of reoxygenation (to 81.8 (2.6) mm Hg) and remained at a lower level throughout the reoxygenation period. In hearts that received halothane during the first 30 min of reoxygenation, LVSP was reduced during the first 30 min and then increased after discontinuation of halothane to values not different from baseline.

METABOLIC MEASUREMENTS

Creatine kinase

In untreated control hearts, CK release, as an indicator of cell damage, did not increase significantly during anoxic perfusion but increased markedly during the early reoxygenation phase with a peak value (149.1 iu min^{-1} g^{-1}) at 1 min of reoxygenation (fig. 3, bottom). CK release was increased in control hearts during the first 40 min of reoxygenation. In hearts treated with halothane during anoxia, maximum CK release was reduced to 33.7 % compared with control hearts and in hearts treated with halothane only during early reoxygenation to 6.7 %. As a consequence, total cumulative CK release (fig. 4) was reduced significantly when halothane was given during reoxygenation (60 (12) iu g^{-1}) compared with untreated controls (712 (52) iu g^{-1}) or hearts treated with halothane during anoxia (188 (8) iu g^{-1}).

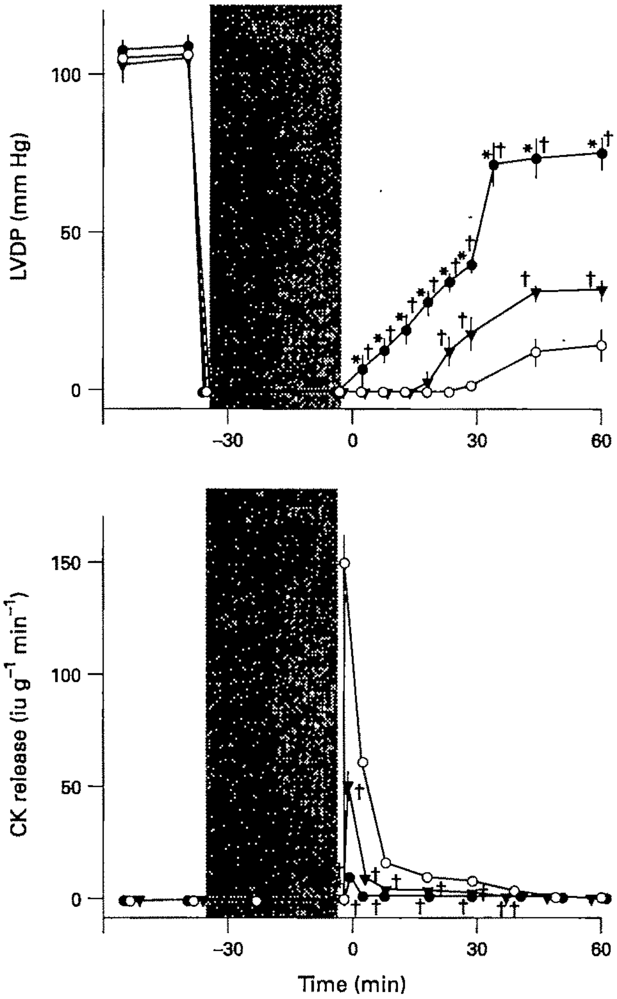


Figure 3 Effect of halothane 0.4 mmol litre^{-1} given during the first 30 min of anoxic perfusion (▼) or during the first 30 min of reoxygenation (●), on left ventricular developed pressure (LVDP) as a variable of myocardial function, and release of creatine kinase (CK) into the coronary venous effluent as a variable of cellular damage (mean, SEM). †$P < 0.05$ *vs* control hearts (○); *$P < 0.05$ halothane–anoxia *vs* halothane–reoxygenation. Top: Functional recovery was best when halothane was given during reoxygenation. Bottom: Major cellular injury, as evident from the release of an intracellular marker enzyme, occurred at the onset of reoxygenation and was reduced most markedly when halothane was present at reoxygenation.

Oxygen consumption

$\dot{V}O_2$ was approximately 1000 µl min^{-1} g^{-1} dry tissue under baseline conditions in all three groups (table 1). In control hearts, $\dot{V}O_2$ increased to 100 % of baseline with the onset of reoxygenation and then decreased to 57.3 % at the end of reoxygenation. In hearts treated with halothane during the anoxic period, $\dot{V}O_2$ was 108 % of baseline at the onset of

Table 1 Effects of halothane in anoxia–reoxygenation experiments. Data are mean (SEM), $n = 5$. LVSP = Left ventricular systolic pressure; CPP = coronary perfusion pressure; $\dot{V}o_2$ = myocardial oxygen consumption. $^*P < 0.05$ compared with untreated hearts (control); $^\dagger P < 0.05$ compared with hearts treated with halothane during anoxia (halothane anoxia)

	LVSP (mm Hg)			CPP (mm Hg)			$\dot{V}o_2$ (μl min^{-1} g^{-1} 10^3)		
	Control	Halothane anoxia	Halothane reoxygenation	Control	Halothane anoxia	Halothane reoxygenation	Control	Halothane anoxia	Halothane reoxygenation
Baseline									
0 min	104.7 (3.8)	102.7 (6.2)	106.6 (3.2)	101.2 (2.1)	104.2 (1.4)	101.8 (0.4)	1.12 (0.05)	1.06 (0.05)	0.99 (0.02)
15 min	107.1 (2.6)	103.7 (5.9)	111.0 (3.0)	100.6 (1.6)	102.6 (1.8)	102.8 (0.4)	1.10 (0.06)	1.06 (0.04)	0.96 (0.02)
Reoxygenation									
5 min	112.2 (4.3)	81.8 (2.6)*	75.9 (4.1)*	150.0 (5.7)	117.8 (5.9)*	117.0 (0.8)*	1.10 (0.10)	1.15 (0.08)	0.80 (0.05)†
10 min	103.6 (6.1)	69.0 (2.6)*	66.9 (1.7)*	151.2 (6.5)	120.8 (4.9)*	114.8 (0.5)*	0.87 (0.09)	0.94 (0.04)	0.64 (0.07)†*
15 min	97.8 (6.5)	63.6 (2.6)*	65.6 (2.8)*	154.5 (7.9)	121.8 (4.6)*	120.4 (4.3)*	0.81 (0.08)	0.85 (0.04)	0.60 (0.05)†*
30 min	93.4 (7.7)	70.9 (1.7)*	75.5 (5.4)*	161.1 (8.0)	125.8 (7.2)	143.4 (16.2)*	0.67 (0.06)	0.72 (0.05)	0.73 (0.04)
45 min	100.1 (8.3)	76.6 (2.4)*	99.5 (6.4)†	163.9 (9.1)	125.0 (8.1)	123.0 (13.9)*	0.63 (0.03)	0.76 (0.05)	0.77 (0.05)
60 min	101.5 (9.0)	75.9 (4.0)*	99.2 (4.9)†	166.4 (11.0)	127.2 (9.2)	122.2 (13.0)*	0.63 (0.04)	0.75 (0.05)	0.82 (0.04)

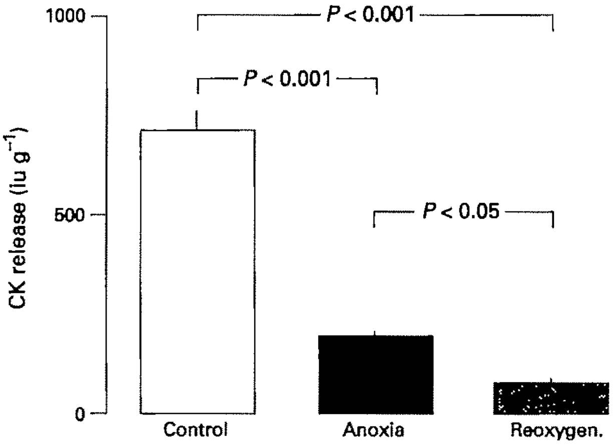


Figure 4 Effect of halothane 0.4 mmol litre^{-1} given during the first 30 min of anoxic perfusion (Anoxia) or during the first 30 min of reoxygenation (Reoxygen.) on the total amount of creatine kinase (CK) released during anoxia and reoxygenation (mean, SEM).

reoxygenation and then decreased to 70.8%. In hearts treated with halothane during the first 30 min of reoxygenation, $\dot{V}o_2$ was lower during the initial reoxygenation period compared with the two other groups; it was 83% of baseline at 5 min reoxygenation and then decreased to 75% at 15 min of reoxygenation. After discontinuation of halothane, $\dot{V}o_2$ increased again in this group, reaching 84% of baseline at the end of the reoxygenation period.

Discussion

We have found, in an isolated rat heart model, that halothane only moderately attenuated myocardial injury during a state of oxygen and substrate deprivation, but had a pronounced protective action on myocardial injury at reoxygenation after an anoxic period.

CRITIQUE OF METHODS

In this study, we used a period of anoxic and substrate-free perfusion to simulate myocardial ischaemia, and subsequent reoxygenation and resupply of metabolic substrates to simulate myocardial reperfusion. Although the terms "reperfusion" and "reoxygenation" and the terms "anoxic perfusion" and "ischaemia" are often used synonymously, some important differences should be taken into account in the interpretation of our results. First, anoxic perfusion was used to allow the possibility of halothane administration during simulated ischaemia. Anoxic perfusion may have attenuated the development of intracellular acidosis and accumulation of intracellular adenosine; *in vivo*, both mechanisms may have some endogenous myocardial protective effects. Second, during buffer perfusion there are no neutrophils and thrombocytes; both may interact with the development of *in vivo* ischaemia–reperfusion injury (for review see [11]). Thus this experimental model excludes some of the (patho)mechanisms that play a role in an *in vivo* ischaemia–reperfusion situation.

In most previous *in vitro* and *in vivo* studies that have found a reduction in myocardial injury in an ischaemia–reperfusion situation in the presence of volatile anaesthetics, the beneficial effects were explained primarily by the action of anaesthesia on sympathoadrenal activity and on myocardial oxygen demand [6, 7, 9], rather than by any intrinsic property of the volatile anaesthetics. Some studies also discussed a protective effect on myocardial reperfusion injury [8, 12], but the interpretation of these data is difficult because halothane was given also before reperfusion (during a period of ischaemia [13], hypoxia [6, 7, 9] or cardioplegic arrest [8]) and often also before the onset of oxygen deprivation (hypoxia [6, 7, 9], ichaemia [13] or cardioplegic arrest [8, 12]). However, it is known that other negative inotropic drugs (e.g. calcium antagonists or β blockers) exert potent anti-ischaemic effects when given before or during ischaemia. As the extent of reperfusion-induced injury is proportional to the severity of the preceding ischaemia, it is impossible from these studies to ascertain if a protective effect is caused by a reduction in reperfusion injury or if it is secondary to an anti-ischaemic action.

In order to reduce haemodynamic side effects in the experimental model used in this study, we controlled heart rate, ventricular volume and coronary flow. Nevertheless, loading conditions between the experimental groups were not identical during reoxygenation; halothane-treated hearts had a higher LVDP and consequently a greater wall stress during reoxygenation compared with untreated controls. However, in the treatment group, myocardial injury was reduced markedly and increased loading conditions should have had the opposite effect. Therefore, differences in loading conditions can be regarded as a "conservative" effect that cannot explain the observed protection.

To differentiate between anti-ischaemic effects and protection against reperfusion injury, halothane was administered only during the first 30 min of anoxia or for the first 30 min of reoxygenation. Because the danger of impending contracture in the reoxygenated myocardial cell is evoked by the reactivation of mitochondrial energy production [14], administration of halothane was started with a 1-min anoxic wash-in of the substance into the perfusion system before reoxygenation in the halothane–reoxygenation group. In the hearts treated with halothane during the anoxic perfusion, halothane was discontinued 5 min before the onset of reoxygenation. Although we found in preliminary experiments in normoxic hearts that a 5-min washout of halothane was sufficient for complete reversal of the haemodynamic effects of halothane, it should be taken into consideration that an unknown amount of halothane may have been present at the onset of reoxygenation in this group. Therefore, some protection against reoxygenation-induced injury may have been present in addition to the anti-ischaemic effect in this experimental group.

INTERPRETATION OF RESULTS

In the ischaemia–reperfusion model used in this study, the manifestation of lethal cell injury occurs at the onset of reoxygenation, as evident from the massive release of creatine kinase, an intracellular marker enzyme. Because the extent of this injury can be reduced through an intervention at the time when oxygen is re-supplied, cell injury represents not only the manifestation of ischaemic injury, but in part true "reperfusion injury" in the sense defined by Rosenkranz and Buckberg [1] as "metabolic, functional and structural consequences of restoring coronary arterial flow...that can be avoided or reversed by modifications of the conditions of reperfusion". The mechanisms underlying the type of "reperfusion injury" that occurs in the present model have been studied in the past years; one important mechanism is cellular contracture that occurs at reoxygenation and most likely results from the combination of a high cytosolic calcium concentration, accumulated during the anoxic period, and the re-supply of metabolic energy with the onset of reoxygenation (for review, see [15]). Contracture may result in mechanical disruption of the cells [15] that have an increased mechanical fragility after the period of energy depletion [16]. Consequently, in the isolated heart model used in this study, reoxygenation induced a sudden increase in LVEDP (contracture) and a high myocardial oxygen consumption. Simultaneously, there was a massive release of creatine kinase. Oxygen consumption decreased to approximately 57% of baseline values, probably an effect of the reduced amount of viable myocardium. These findings were identical to others in similar models [17–19].

When present at the critical moment of reoxygenation, halothane had a pronounced protective effect against this type of "reperfusion injury"; it completely prevented the development of contracture and reduced the peak release of creatine kinase to 6.7% of that seen in untreated hearts. In addition, myocardial oxygen consumption was reduced compared with untreated controls despite an increased mechanical work index (LVDP). From these results it seems likely that the protective effect of halothane against "reperfusion injury" consists of attenuation of cellular contracture.

It was clearly beyond the scope of the study to identify the cellular mechanisms of the protective effect of halothane against reperfusion-induced contracture. However, in parallel with the recent understanding of the underlying pathophysiology, some protective mechanisms have been identified, and from the mechanisms of action that have been described for halothane in normal myocardium, several protective mechanisms against contracture development are possible. First, contractile inhibition at the level of the myofibrils. It has been shown previously that temporary block of the contractile apparatus (using the substance BDM) can prevent or reduce "reperfusion injury" in isolated cardiomyocytes [20], isolated hearts [17] and intact hearts [21]. Even partial contractile inhibition (by SIN-1C) had a protective effect in isolated hearts [18] and *in vivo* [22], probably by reducing developed force in the re-energized cardiomyocyte below a critical threshold [22]. A reduction in the calcium sensitivity of myofibrils by halothane has been described [23, 24] and the resulting contractile inhibition may have contributed to the observed protective effect.

Second, effects on intracellular calcium. The high intracellular calcium concentration accumulated during the ischaemic period represents the trigger for cellular contracture during reperfusion. With the onset of reperfusion, intracellular calcium may increase even further by calcium influx via the Na^+–Ca^{2+} exchanger [25], and phasic oscillations of intracellular calcium occur as a result of pathological calcium cycling by the sarcoplasmic reticulum [26]; both mechanisms can increase further contractile activation. In normal myocardium, inhibition of the Na^+–Ca^{2+} exchanger by halothane has been shown [27]. In addition, halothane interferes with the calcium handling of the sarcoplasmic reticulum (of normal myocardium) by direct inhibition of sarcoplasmic function [28] and an action on the calcium-dependent calcium-release channel [29]. At low intracellular pH and ATP concentrations (conditions similar to early reperfusion), halothane may have an opposite effect on sarcoplasmic reticulum calcium handling, enhancing calcium uptake [30]. Halothane may also interact with the Na^+–H^+ exchange mechanism, as has been shown in the erythrocyte model [31]. Inhibition of the Na^+–H^+ exchanger at reperfusion preserves intracellular acidosis, prevents pathological calcium cycling [32] and protects myocardial structure and function [19]. Halothane also inhibits calcium influx via the voltage-dependent calcium channel and this may be an important mechanism for the reduction of myocardial contractility by halothane in normal myocardium [33]; but for the development of reperfusion injury the voltage-dependent calcium channel may play only a minor role [15]. It should be taken into account that the cellular mechanisms of action mentioned above have been shown for halothane in normal myocardium or cellular organelles isolated from normal myocardium and that the possible protective effects mentioned on the pathomechanisms of reperfusion injury remain speculative. However, this study provides evidence that the main protective mechanism must be involved in the prevention of reoxygenation-induced cellular contracture. The mechanisms of action of halothane on ischaemic-reoxygenated myocardium are now under investigation.

Besides the markedly reduced cellular injury at the onset of reoxygenation, the hearts showed a faster and better functional recovery when halothane was given during reoxygenation in a concentration that reduced LVDP as a variable of contractility in normal hearts by about 50%. The improved functional recovery may be simply the result of a greater amount of viable myocardium in these hearts because of the reduction of lethal reperfusion injury. In addition, a direct influence on non-lethal cell injury that results in post-ischaemic myocardial dysfunction (myocardial stunning) must also be discussed; *in vivo*, such attenuation of myocardial stunning has been found in different experimental models [13, 34, 35].

Halothane was also protective when given during anoxic perfusion (reduced creative kinase release and improved functional recovery), but the protective effect was smaller. A beneficial role of volatile anaesthetics during myocardial ischaemia was observed in 1969 by Spieckermann and colleges [36], who found a prolonged tolerance to global ischaemia and enhanced preservation of high energy compounds in dog hearts. It was shown recently that halothane slows calcium accumulation during "ischaemia" [12]. Consequently, the level of diastolic tension was reduced in the present model. However, reoxygenation-induced contracture still occurred in these hearts and initial $\dot{V}O_2$ during reoxygenation was high despite a reduced myocardial work index. Thus the hearts showed typical signs of reperfusion injury, although the extent of reperfusion injury was reduced. As the latter depends mainly on the severity of the preceding ischaemia, the presence of halothane during an ischaemic period seems to attenuate ischaemic injury. This is also in accordance with the findings of Lochner and co-workers [12], who found reduced cellular damage when halothane was given during cardioplegic arrest to isolated rat hearts.

Acknowledgement

We thank Mr Husmann from the Max Planck Institute for Carbon Research, Mühlheim, Germany, for his help with the design of the method of halothane administration and for measurements of halothane concentrations. The help of Professor Novotny, Institut für Anatomie, Heinrich-Heine Universität Düsseldorf, Germany is also gratefully acknowledged.

References

1. Rosenkranz ER, Buckberg GD. Myocardial protection during surgical coronary reperfusion. *Journal of the American College of Cardiology* 1983; **1**: 1235–1246.
2. Cope DK, Impastato WK, Downey JM. Inhalational anesthesia protects the ischemic myocardium from infarction. *Anesthesiology* 1994; **81**: A672.
3. David RF, DeBoer LW, Rude RE, Lowenstein E, Maroko PR. The effect of halothane anesthesia on myocardial necrosis, hemodynamic performance, and regional myocardial blood flow in dogs following coronary artery occlusion. *Anesthesiology* 1983; **59**: 402–411.
4. Kissin I, Stanbridge R, Bishop SP, Reves JG. Effect of halothane on myocardial infarct size in rats. *Canadian Anaesthetists Society Journal* 1981; **28**: 239–243.
5. Gomez MN, Brown P, Moyers JR, Carter JG, Tinker JH. Effect of halothane on infarct size in swine with coronary collateral circulation. *Anesthesiology* 1986; **65**: A55.
6. Buljubasic N, Stowe DF, Marijic J, Roerig DL, Kampine JP, Bosnjak ZJ. Halothane reduces release of adenosine, inosine, and lactate with ischemia and reperfusion in isolated hearts. *Anesthesia and Analgesia* 1993; **76**: 54–62.
7. Buljubasic N, Marijic J, Stowe DF, Kampine JP, Bosnjak ZJ. Halothane reduces dysrhythmias and improves contractile function after global hypoperfusion in isolated hearts. *Anesthesia and Analgesia* 1992; **74**: 384–394.
8. Coetzee A, Brits W, Genade S, Lochner A. Halothane does have protective properties in the isolated ischemic rat heart. *Anesthesia and Analgesia* 1991; **73**: 711–719.
9. Marijic J, Stowe DF, Turner LA, Kampine JP, Bosnjak ZJ. Differential protective effects of halothane and isoflurane against hypoxic and reoxygenation injury in the isolated guinea pig heart. *Anesthesiology* 1990; **73**: 976–983.
10. Abel FL. Maximal negative dP/dt as an indicator of end of systole. *American Journal of Physiology* 1981; **240**: H676–H679.
11. Mullane KM, Young M. The contribution of neutrophil activation and changes in endothelial function to myocardial ischemia–reperfusion injury. In: Yellon DM, Jennings RB, eds. *The Pathophysiology of Reperfusion and Reperfusion Injury*. New York: Raven Press, 1992; 59–83.
12. Lochner A, Harper IS, Salie R, Genade S, Coetzee AR. Halothane protects the isolated rat myocardium against excessive total intracellular calcium and structural damage during ischemia and reperfusion. *Anesthesia and Analgesia* 1994; **79**: 226–233.
13. Coetzee A, Moolman J. Halothane and the reperfusion injury in the intact animal model. *Anesthesia and Analgesia* 1993; **76**: 734–744.
14. Piper HM. Mitochondrial injury in the oxygen-depleted and reoxygenated myocardial cell. IN: Piper HM, ed. *Pathophysiology of Severe Ischemic Injury*. Dordrecht: Kluwer Academic, 1990; 91–114.
15. Siegmund B, Schlüter, KD, Piper HM. Calcium and the oxygen paradox. *Cardiovascular Research* 1993; **27**: 1778–1783.
16. Ganote CE, Sims MD, Safavi S. Effects of dimethylsulfoxide (DMSO) on the oxygen paradox in perfused rat hearts. *American Journal of Pathology* 1982; **109**: 270–276.
17. Schlüter KD, Schwartz P, Siegmund B, Piper HM. Prevention of the oxygen paradox in hypoxic-reoxygenated hearts. *American Journal of Physiology* 1991; **261**: H416–H432.
18. Schlüter K-D, Weber M, Schraven E, Piper HM. NO donor SIN-1 protects against reoxygenation-induced cardiomyocyte injury by a dual action. *American Journal of Physiology* 1994; **267**: 1461–1466.
19. Hendrikx M, Mubagwa K, Verdonck F, Overloop K, Van Hecke P, Vanstapel F, Van Lommel A, Verbeken E, Lauweryns J, Flameng W. New Na^+–H^+ exchange inhibitor HOE 694 improves post-ischemic function and high-energy phosphate resynthesis and reduces Ca^{2+} overload in isolated perfused rabbit heart. *Circulation* 1994; **89**: 2787–2798.

20. Siegmund B, Klietz T, Schwartz P, Piper HM. Temporary contractile blockade prevents hypercontracture in anoxic-reoxygenated cardiomyocytes. *American Journal of Physiology* 1992; **260**: H426–H435.
21. Schlack W, Uebing A, Schäfer M, Schäfer S, Piper HM, Thämer V. Regional contractile blockade at the onset of reperfusion reduces infarct size in the dog heart. *Pflügers Archiv, European Journal of Physiology* 1994; **428**: 134–141.
22. Schlack W, Uebing A, Schäfer M, Bier F, Grunert S, Ebel D, Piper HM, Thämer V. Intracoronary SIN-1C during reperfusion reduces infarct size in dog. *Journal of Cardiovascular Pharmacology* 1995; **25**: 424–431.
23. Murat I, Ventura-Clapier R, Vassort G. Halothane, enflurane, and isoflurane decrease calcium sensitivity and maximal force in detergent treated cardiac fibers. *Anesthesiology* 1988; **69**: 892–899.
24. Tavernier BM, Adnet PJ, Imbenotte M, Etchrivi TS, Reyford H, Haudecoeur G, Scherpereel P, Krivosic-Horber RM. Halothane and isoflurane decrease calcium sensitivity and maximal force in human skinned cardiac fibers. *Anesthesiology* 1994; **80**: 625–633.
25. Kihara Y, Sasayama S, Inoko M, Morgan JP. Sodium/calcium exchange modulates intracellular calcium overload during post-hypoxic reoxygenation in mammalian working myocardium. Evidence from aequorin-loaded ferret ventricular muscles. *Journal of Clinical Investigation* 1994; **93**: 1275–1284.
26. Siegmund B, Zude R, Piper HM. Recovery of reoxygenated cardiomyocytes from severe Ca^{2+} overload. *American Journal of Physiology* 1992; **263**: H1262–H1269.
27. Haworth RA, Goknur AB. Inhibition of sodium/calcium exchange and calcium channels of heart cells by volatile anesthetics. *Anesthesiology* 1995; **82**: 1255–1265.
28. Komai H, Rusy BF. Direct effect of halothane and isoflurane on the function of the sarcoplasmic reticulum. *Anesthesiology* 1990; **72**: 694–698.
29. Lynch C III, Frazer MJ. Anaesthetic alteration of ryanodine binding by cardiac calcium release channels. *Biochimica et Biophysica Acta* 1994; **1194**: 109–117.
30. Blanck TJJ, Thompson M. Calcium transport by cardiac sarcoplasmic reticulum: modulation of halothane action by substrate concentration and pH. *Anesthesia and Analgesia* 1981; **60**: 390–394.
31. Kracke GR, Drake RK. Halothane, enflurane, and isoflurane inhibit sodium/proton exchange in mammalian erythrocytes. *Annals of the New York Academy of Sciences* 1991; **625**: 780–783.
32. Ladilov YV, Siegmund B, Piper HM. Protection of reoxygenated cardimyocytes against hypercontracture by inhibition of Na$^+$/H$^+$ exchange. *American Journal of Physiology* 1995; **268**: H1531–H1539.
33. Lee DL, Zhang J, Blanck TJJ. The effect of halothane on voltage-dependent calcium channels in isolated Langendorff-perfused rat heart. *Anesthesiology* 1994; **81**: 1212–1219.
34. Warltier DC, Al-Wathiqui MH, Kampine JP, Schmeling WT. Recovery of contractile function of stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane. *Anesthesiology* 1988; **69**: 552–565.
35. White JL, Myers AK, Analouei A, Kim YD. Functional recovery of stunned myocardium is greater with halothane than fentanyl anaesthesia in dogs. *British Journal of Anaesthesia* 1994; **73**: 214–219.
36. Spieckermann PG, Brückner JB, Kübler W, Lohr B, Bretschneider HJ. Preischemic stress and resuscitation time of the heart. *Verhandlungen der Deutschen Gesellschaft für Herz- und Kreislaufforschung* 1969; **33**: 358–364.

British Journal of Anaesthesia 1996; **76**: 868–869

SHORT COMMUNICATIONS

Occupational x-ray exposure of anaesthetists

C. McGowan, B. Heaton and R. N. Stephenson

Summary

Lithium fluoride thermoluminescent dosimeter chips were used to measure the radiation dose received by anaesthetists caused by the use of image intensification during a typical 4-week period in an orthopaedic theatre. These were used to estimate an annual dose, for comparison with dose limits, to ascertain if anaesthetists should be included in personnel monitoring services. Doses proved to be below detectable limits; hence anaesthetists are at minimal risk from occupational exposure to radiation. The orthopaedic theatre is believed to use more x-rays than other theatres, so exposure elsewhere should also be undetectable. *(Br. J. Anaesth.* 1996; 868–869)

Key words

Anaesthetist, risks. Operating rooms, contamination.

Although anaesthetists can frequently be exposed to ionizing radiation, in the form of scatter from diagnostic x-rays used during some theatre procedures, little work has been done to determine the level of exposure and whether or not they might be at risk. It is generally assumed that the doses are very low, and consequently anaesthetists are often not included in radiation protection personnel monitoring services. In this study we tested this assumption of negligible exposure.

Previous studies [1–3] relating to dose measurements in anaesthetists have tended to address the issue as incidental to measurements on the patient and other theatre staff, often examining exposures incurred during specific procedures only, rather than obtaining an assessment of total annual exposures caused by all work. Such an assessment could then be used as a basis for the decision as to whether or not anaesthetists should be included in personnel monitoring services.

Methods and results

Careful consideration was given to the best way in which to obtain a reasonable estimate of the annual dose. To this end, advice was sought from anaesthetists, radiographers and theatre staff as to the operating theatres in which most x-rays were used. The conclusion reached was that orthopaedic theatres used the most x-rays, and it was decided to measure the doses received in the orthopaedic trauma theatre. If these doses proved to be low, it was felt that it could be concluded that doses in other theatres would also be low, and hence no anaesthetist would be at risk.

A period of 4 weeks was devoted to the initial measurements in the trauma theatre. The total number of operations performed during this time and the number using x-rays were noted, and compared with the same values (obtained from theatre records) for the 4 months before the start of the study. It was possible to show that the period of study was typical as regards the use of x-rays, and thus the doses meaured could be extrapolated to provide a reasonable estimate of the annual dose received by anaesthetists in theatre.

All dose measurements were made using lithium fluoride thermoluminescent dosimeter (TLD) chips (TLD 100, Harshaw Chemical Company). These were selected for their low dose threshold, reasonable tissue equivalence, and small size, so that the wearers would not be unduly inconvenienced. These chips had a minimum detectable dose of 0.1 mSv.

It was suspected that the dose received by the anaesthetist during a single operation or even during a single working session would be too low to measure, and hence it was decided to conduct the measurement continuously over 4 individual weeks and also for the 4 weeks together, in the event that the weekly dose was below the detection limit. This was achieved by transferring the dosimeters between anaesthetists, to obtain cumulative weekly and monthly dose meaurements. Doses were monitored only during the day, from Monday to Friday; the weekend and evening operations were excluded. In reality, an individual anaesthetist would only work a maximum of about two sessions per week in the trauma theatre at Aberdeen Royal Infirmary (excluding emergency hours) and therefore an estimate of the annual dose from the above would be a "worst case scenario" value for the hypothetical situation of a single anaesthetist working in theatre all of the time.

Six positions were selected at which the doses would be measured. These were the forehead, to obtain an estimate of the eye dose as the lens of the eye is vulnerable to ionizing radiation; thyroid;

C. McGowan, bsc, msc, B. Heaton, msc, phd, Department of BioMedical Physics and BioEngineering, University of Aberdeen. R. N. Stephenson, mbchb, frca, Department of Anaesthetics, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB9 2ZD.
Accepted for publication: February 1, 1996.
*Present address for correspondence: Department of Physics and Astronomy, University of St Andrews, North Haugh, St Andrews, Fife KY16 9SS.

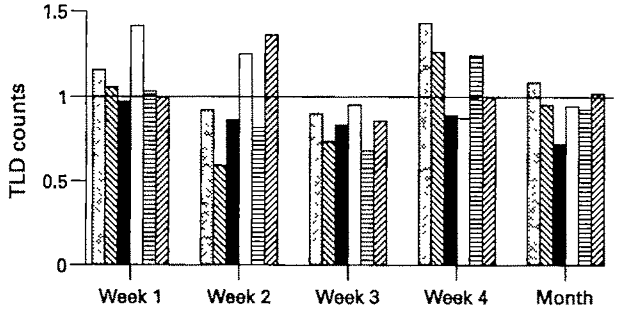


Figure 1 Total number of counts, including background, recorded on the lithium fluoride thermoluminescent dosimeter (TLD) chips worn by the anaesthetists, compared with the average background counts. ◫ = Over apron, ▧ = under apron, ■ = right side, □ = left side, ▤ = eye, ▨ = thyroid.

torso, to provide a measure of the whole body dose, both under and outside the protective lead rubber aprons worn when x-rays are used in theatre; and on the left and right sides of the body, where the lead apron does not always fasten securely. Thus at any one time the anaesthetist wore 12 TLD; six to measure the weekly dose and six to measure the monthly dose.

All TLD used for the experiment were initially read out at the same time and all started accumulating a background dose from that time. After completion of the individual exposure periods, the TLD were read after an interval of 24 h rather than waiting until the end of the experiment and reading all at the same time. (In the latter case background TLD are normally kept for the full duration of the experiment and on reading out a constant background dose rate is assumed.) This readout method was adopted, partly because time constraints implied that any procedural changes had to be implemented rapidly but also to reduce variations in signal fading which may have occurred if low doses were received. In order to measure the background, a group of 21 TLD was selected, kept initially for 7 days, and every 3 days, three were read out and the average value calculated. Thus it was possible to determine approximately by the way in which the background signal built up with time, and hence calculate the expected number of background counts on a TLD that had been used for a measurement. The calculated value is only an estimate as the total background level consists of counts produced by background radiation, and a signal inherent in the TLD which varies slightly between chips, so real background count values fluctuate around the estimated level.

Figure 1 shows the counts detected by each of the TLD during each week and for the whole month. These values are inclusive of the background counts, and each is shown normalized to the estimated background count value for that particular group of TLD. The background value is represented by the horizontal line.

As can be seen from the histogram, the recorded counts fluctuated approximately equally above and below the background level, as would occur if no doses were recorded, because of the variation in the inherent signals on the chips. Thus the dose received by the anaesthetists, even over the course of a month, was below or approximately equal to the limit of detection of the TLD.

Comment

As it was shown that the 4 weeks of the study had a typical distribution of operations involving x-rays, the doses recorded in those 4 weeks could be used to estimate an annual dose. However, as the measured dose was below the detection limit, it was effectively zero, and therefore this estimate cannot be made accurately. But even though the monthly dose was undetectable, the annual dose may reach detectable levels, and a more extended study would be needed to determine if this is the case. However, such a study would not be necessary as if the monthly dose is undetectable, the annual dose must be extremely small, and negligible compared with the recommended dose limit of the Ionizing Radiations Regulations of 15 mSv year^{-1} for a non-classified radiation worker [4], and also to future recommendations of the International Commission on Radiological Protection [5]. Moreover, because it is generally agreed that trauma theatres use more x-rays than any other operating theatre, the dose received in other theatres should be even smaller. Over the course of a year an anaesthetist moving between theatres should receive a negligible dose of ionizing radiation and thus is not at risk. Hence it is not necessary to include anaesthetists in personnel monitoring services.

References

1. Trachtenberg HA, Slater EM. Anaesthetists' exposure to radiation during radium implantation procedures. *Journal of the American Medical Association* 1965; **191**: 763–764.
2. Jain MP, Nagaratnam MA, Ghosh D. Assessment with TLD of radiation exposure to staff during radium insertions in cancer of cervix. *British Journal of Radiology* 1980; **53**: 1083–1086.
3. Berthelsen B, Cederblad A. Radiation doses to patients and personnel involved in embolization of intracerebral arteriovenous malformations. *Acta Radiologica* 1991; **32**: 492–497.
4. The Ionising Radiations Regulations 1985. London: HMSO, 1985.
5. ICRP Publication 60, 1990. Recommendations of the International Commission on Radiological Protection. Oxford: Pergamon Press, 1991.

British Journal of Anaesthesia 1996; **76**: 870–871

Total i.v. anaesthesia for transcranial magnetic evoked potential spinal cord monitoring

J. W. H. Watt, M. H. Fraser, B. M. Soni, P. K. Sett and R. Clay

Summary

Continuous intraoperative monitoring of transcranial magnetic motor evoked potentials (TcMMEP) can warn the surgeon of motor tract damage more effectively than somatosensory evoked potentials. As a non-invasive technique it is especially useful during post-traumatic internal fixation and is applicable whatever the level of the spinal cord at risk. Inhalation and many i.v. anaesthetics block the single pulse TcMMEP but a total i.v. anaesthetic regimen based on methohexitone, alfentanil and ketamine was effective in seven patients undergoing post-traumatic internal fixation. Consistent TcMMEP of 100–1000 mcV were obtained in all patients, with a latency change of only 2 ms above preoperative values. Good cardiovascular stability was maintained during operation. (*Br. J. Anaesth.* 1996; **76**: 870–871).

Key words

Anaesthetics, i.v. monitoring, evoked potentials. Spinal cord, evoked potentials.

Spinal column surgery is associated with a risk of permanent neurological damage and it is imperative to monitor reliably and repetitively the integrity of the long motor tracts throughout surgery and before operation. Dependence on the use of somatosensory evoked potentials may give a false sense of security [1]. Currently, difficulties in obtaining responses in anaesthetized patients [2, 3], even in the absence of neuromuscular block, are impeding wider adoption of transcranial magnetic motor evoked potential (TcMMEP) monitoring. Previous unpublished work at this centre established that a combination of ketamine, alfentanil and etomidate permitted TcMMEP monitoring. A recent publication of experimental work in dogs demonstrated that methohexitone also had a permissive effect in this situation [4], despite contrary effects with thiobarbiturates.

The aim of this study, therefore, was to use a reliable total anaesthesia (TIVA) regimen for spinal surgery with intraoperative TcMMEP monitoring.

Method and results

In seven adult patients undergoing internal fixation of the spinal cord after spinal column trauma, we recorded continuous intraoperative TcMMEP from a suitable muscle. Selection of the latter depended on the level of neurological injury and was either below the fracture in patients in whom the muscle was neurologically intact or incomplete ($n = 3$), or on the last intact myotome of neurologically complete lesions ($n = 4$). Two patients had cervical injuries and the remainder thoracolumbar. The stimulus was provided by a Magstim model 200 single pulse machine using a double 70-m cone coil which produces a peak magnetic field strength of 2.0 Ta. Recordings were made using a Medelec MS 91a machine. Peak-to-peak voltage and latencies were assessed continuously and compared with preoperative values. As voltage responses are always less during anaesthesia, the Magstim output of 100% was usually used in the intraoperative period.

Patients were premedicated with either promethazine or morphine, deliberately avoiding benzodiazepines [3]. The anaesthesia regimen comprised a bolus dose of methohexitone 2 mg kg^{-1} for hypnosis, followed by 100 µg kg^{-1} for 30 min and then 75–50 µg kg^{-1} min^{-1}. Analgesia was provided by a bolus dose of alfentanil 50 µg kg^{-1} followed by 5 µg kg^{-1} min^{-1} for 15 min and 1 µg kg^{-1} min^{-1} thereafter. Ketamine was used in a low dose of 20 µg kg^{-1} min^{-1} decreasing to 14 µg kg^{-1} min^{-1} after 1 h, to augment anaesthesia and improve TcMMEP amplitude responses [5]. One bolus of a neuromuscular blocking agent was used in most instances at induction of anaesthesia for initial airway control, but before recording TcMMEP, subsequent recovery of neuromuscular function was confirmed using a conveniently located peripheral motor nerve. The adequacy of the TIVA-based anaesthesia was assessed with familiarity according to cardiovascular stability with the aid of invasive arterial pressure monitoring, and by the absence of reflex body movements in response to surgical stimuli. All patients were awakened within 30 min of discontinuation of the TIVA, albeit with the aid of doxapram or naloxone, and none had psychomimetic side effects from ketamine.

Reliable TcMMEP were obtained in all patients using this TIVA regimen, latencies being within 2 ms of preoperative values. When anaesthesia in an individual patient was optimized, if necessary even by elimination of 25% nitrous oxide from the air and

---

J. W. H. Watt, MB, CHB, FRCA, MD, M. H. Fraser, MB, CHB, FRCS, B. M. Soni, MB, BS, MS(NEURO), P. K. Sett, MB, BS, MS, FRCS, FRCS(SN), R. Clay, Spinal Injuries Unit, Southport and Formby NHS Trust Hospital, Town Lane, Southport, Merseyside PR8 6PN. Accepted for publication: February 6, 1996.

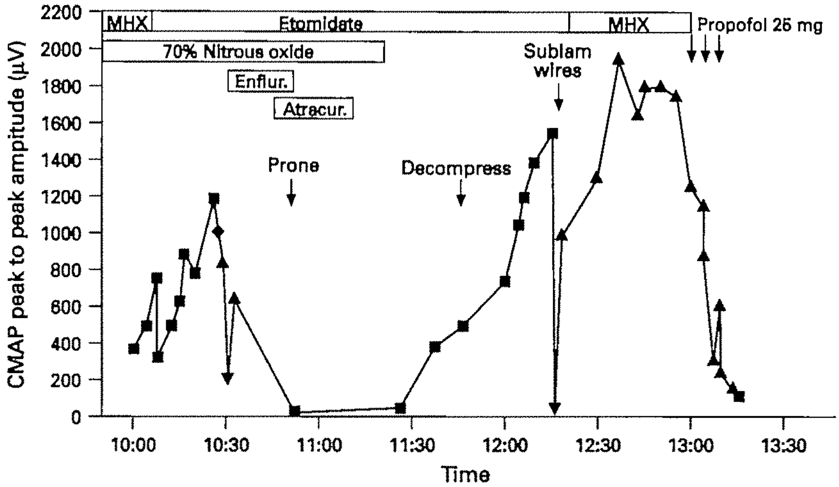


Figure 1 Compound muscle action potential from the tibialis anterior in patient No. 1 produced by transcranial magnetic motor stimulation during total i.v. anaesthesia with methohexitone (MHX), etomidate or propofol. ■ = 100% Magstim output, ◆ = 90% output, ▲ = 80% output, ▼ = 70% output.

oxygen mixture, voltage was at least 100 mcV in all patients. It was noticeable in many cases that TcMMEP increased permanently after surgical decompression of the compromised spinal cord (Fig. 1). There was a temporary loss of TcMMEP in two patients after passage of sublaminar wires but no patient sustained neurological deterioration after operation. Two factors affecting TcMMEP amplitude during surgery were variation in the intensity of the surgical stimulus and changes in the position of the hand-held stimulation coil. However, rogue weak TcMMEPs were discounted by repeating stimuli every 2–5 min and examining the stability of the latency.

Comment

Before this series in which methohexitone proved successful, etomidate was the principal hypnotic, used after consultation with the Medicines Control Agency and after local Ethics Research Committee approval. A direct comparison was made between etomidate and methohexitone in patient No. 1 in this series and as there were comparable TcMMEP with both agents (fig. 1), etomidate was abandoned thereafter, although 24-h tetracosactrin responses had recovered in seven patients with an etomidate-based regimen.

Propofol and inhalation agents are powerful suppressants of both magnetic and electrical transcranial evoked potentials, as confirmed in patient No. 1 (fig. 1). The evidence suggests that this effect takes place at the spinal motoneurone or interneurone [2]. While the next generation of magnetic stimulators use the summation effect from double or quadruple pulsing and are better able to overcome anaesthetic-induced TcMMEP depression [6], our experience indicates that the methohexitone-based TIVA regimen provides the greatest potential for non-invasive monitoring of spinal motor tract integrity and would cause less hypotension than propofol. The exact role of ketamine has yet to be clarified.

Acknowledgements

We thank the Magstim company for their help, and Carol McClay.

References

1. Owen JH, Laschinger J, Bridwell K, Shimon S, Nielson C, Dunlap J, Kain C. Sensitivity and specificity of somatosensory and neurogenic evoked potentials in animals and humans. *Spine* 1988; 10: 1111–1118.
2. Zentner J, Ebner A. Nitrous oxide suppresses the electromyographic response evoked by electrical stimulation of the motor cortex. *Neurosurgery* 1989; 24: 60–62.
3. Kalkman CJ, Drummond JC, Ribberink AA, Patel PM, Sano T, Bickford RG. Effects of propofol, etomidate, midazolam, and fentanyl on motor evoked responses to transcranial electrical or magnetic stimulation in humans. *Anesthesiology* 1992; 76: 502–509.
4. Young SS, Boermans HJ, Sylvestre AM. Magnetic motor evoked potentials during methohexital anesthesia in the dog. *Neurosurgery* 1994; 34: 490–495.
5. Ghaly RF, Stone JF, Aldrete A, Levy WJ. Effects of incremental ketamine hydrochloride on motor evoked potentials (MEPs) following transcranial magnetic stimulation: a primate study. *Journal of Neurosurgical Anesthesiology* 1990; 2: 79–85.
6. Taylor BA, Fennelly ME, Taylor A, Farrel F. Temporal summation—the key to motor evoked potential spinal cord monitoring in humans. *Journal of Neurology, Neurosurgery and Psychiatry* 1993; 56: 104–106.

British Journal of Anaesthesia 1996; **76**: 872–873

Spinal clonidine produces less urinary retention than spinal morphine

M. GENTILI AND F. BONNET

Summary

We have conducted a double-blind, randomized study in two groups of 20 patients each, undergoing hip surgery during spinal anaesthesia, to compare the incidence of urinary retention after spinal morphine or clonidine. Patients received 0.5% spinal bupivacaine 15 mg combined with either clonidine 75 µg or morphine 0.2 mg. After operation, patients were examined for micturition, bladder distension, or both; when they failed to void, they received naloxone 0.2 mg, and if bladder distension persisted, a catheter was inserted. At 12 h, all patients in the morphine group but only five in the clonidine group had bladder distension, and at 24 h this was present in seven and one patient in the morphine and clonidine groups, respectively ($P < 0.001$). Naloxone was given in 16 and one, and a catheter was placed in one and six patients in the morphine and clonidine groups, respectively ($P < 0.001$). We conclude that spinal clonidine impaired bladder function to a lesser extent than morphine. (*Br. J. Anaesth.* 1996; **76**: 872–873)

Key words

Anaesthetic techniques, subarachnoid. Analgesics opioid, morphine. Complications, urinary retention. Sympathetic nervous system, clonidine.

Urinary retention is common after spinal administration of opioids [1, 2]; it may be distressing and is a serious limitation to the use of spinal opioids in daily practice, especially in orthopaedic surgery where patients do not routinely have a bladder catheter.

Spinal clonidine strengthens local anaesthetic block and produces postoperative analgesia, with side effects such as hypotension, bradycardia and sedation, but there are no reports of urinary retention [3]. If spinal clonidine is unlikely to promote urinary retention in postoperative patients, it could be an alternative to spinal morphine when bladder catheterization is considered harmful. In this study we tested the hypothesis that spinal bupivacaine with clonidine resulted in a lower frequency of urinary retention than spinal bupivacaine with morphine.

Methods and results

After obtaining informed consent and Ethics Committee approval, we studied 40 ASA II–III patients undergoing hip surgery. Patients were excluded if they were receiving drugs which may interfere with clonidine or morphine, or if they had pathology of the urinary tract.

Patients were premedicated with flunitrazepam 1 mg orally, and allocated randomly to one of two groups. All received spinal 0.5% isobaric bupivacaine 15 mg (3 ml); in addition, patients were given spinal morphine 0.2 mg (group M) or clonidine 75 µg (group C). Maximal extension of the anaesthetic block was evaluated by pinprick.

Ringer's lactate solution was infused at a rate of 15 ml kg^{-1} h^{-1} during surgery and at 3 ml kg^{-1} h^{-1} after operation for 24 h. Blood loss was replaced during surgery with colloids and autologous blood. When hypotension (decrease in systolic arterial pressure $>30\%$ of control value). or bradycardia (heart rate < 50 beat min^{-1}) occurred, doses of ephedrine 6–12 mg i.v. were administered. Atropine was not used. Postoperative pain treatment included propacetamol i.v.

After operation, patients were examined at 6, 12 and 24 h by a blinded observer. At each time, micturition within the preceding hours was noted, and the bladder was examined for distension. When bladder distension was noted, patients were asked to void. If they failed, or if a second examination revealed persistent bladder distension after incomplete micturition, they received naloxone 0.2 mg. If naloxone did not result in complete voiding, the bladder was catheterized transiently.

Results are expressed as mean (SD). Data were analysed using one-way ANOVA and a Student's t test, and chi-square test and Yates' correction and Fisher's exact test where appropriate.

There were 20 patients in each group. The two groups were comparable in age (group C, 64.8 (range 41–77) yr and group M, 61.2 (44–70) yr), weight (77.6 (SD 13.3) kg and 72.9 (11.4) kg) and height (169 (5) cm and 166 (6) cm) (ns). Group C included 16 men and four women and group M, 13 men and seven women. Maximum extension of block was comparable in the two groups. Duration of surgery was 95.8 (8.7) min and 100.9 (15.7) min in groups C and M, respectively (ns). Mean amounts of i.v. infusions were comparable in the peroperative period

---

MARC GENTILI, MD, Clinique Saint Vincent, Rennes, France. FRANCIS BONNET*, MD, Département d'Anesthésie, Hôpital Henri Mondor, Créteil, France. Accepted for publication: January 15, 1996.

*Address for correspondence: Département d'Anesthésie, Hôpital Henri Mondor, 51 avenue du Maréchal de Lattre de Tassigny, 94000, Créteil, France.

Table 1 Incidence of urinary retention (number of patients). *$P < 0.05$ between groups

	Time after operation (h)		
	6	12	24
Bladder distension			
Group C	0	5*	1*
Group M	2	20	7
Bladder catheterization			
Group C	0	1*	0
Group M	0	4	2

(2684 (730) ml and 2875 (428) ml in groups C and M, respectively), and after operation (6055 (1392) ml and 6500 (875) ml in groups C and M). Ephedrine was given to five patients in group C and to three in group M.

At 6 h no patient had experienced spontaneous micturition. At 12 h, 17 patients in group C but none in group M had experienced spontaneous micturition. At 24 h, 20 patients in group C and 12 in group M reported micturition within the preceding 12 h ($P < 0.001$).

Bladder distension was noticed in two patients in group M and in none in group C at 6 h (table 1). At 12 h, all patients in group M had bladder distension compared with only five patients in group C; at 24 h, seven patients in group M and one in group C had bladder distension ($P < 0.001$) (table 1). All patients were able to void when they had bladder distension but micturition was incomplete in one patient in group C and in 14 in group M at 12 h ($P < 0.05$), and in two patients in group M at 24 h. Consequently, naloxone was given to 16 and one patient in groups M and C, respectively ($P < 0.001$).

Bladder catheterization was performed after naloxone in only one patient who failed to empty his bladder at 12 h (group C), while four and two patients were catheterized at 12 h and 24 h, respectively, in group M ($P < 0.001$) (table 1).

Comment

We have found that the incidence of bladder dysfunction was less when spinal clonidine, instead of morphine, was given with spinal bupivacaine.

A difference in urinary output between the two groups might have explained the difference in urinary retention. We did not measure urinary volumes but previous studies indicated that spinal morphine may decrease urinary output by release of arginine vasopressin [4] and conversely that clonidine has a diuretic effect [5]. Such effects would have favoured bladder distension in group C whereas we observed the opposite effect.

Spinal and extradural opioids are considered risk factors for urinary retention [2]. Extradural morphine induces difficulties in micturition in healthy volunteers [6]. Urinary retention ranges from 42% to 62% in patients who have received spinal or extradural opioids [1, 2].

Activation of the parasympathetic pathways to the detrusor and relief of the somatic input to the external bladder sphincter induce micturition. Activation of the sympathetic outflow to the urinary tract promotes an increase in urethral resistances and depresses detrusor contraction, favouring urinary retention. Spinal opioids acting on spinal or supra spinal mu receptors may depress efferent parasympathetic outflow to the bladder, inhibiting detrusor contractions and micturition reflex for several hours after spinal administration.

Spinal administration of clonidine results in less difficulties in micturition. Alpha$_2$ adrenergic agonists have complex and potentially opposite effects on bladder emptying. Peripheral α_2 adrenergic receptors are documented in the bladder wall, especially at the level of the trigone [2]. Their stimulation induces contraction of the smooth muscle fibres of the internal sphincter tone and therefore increases urethral resistances and impairs voiding. As a small dose was given intrathecally, a peripheral effect of clonidine is unlikely. Spinal clonidine decreases sympathetic tone through a supraspinal and spinal effect (on preganglionic sympathetic neurones) which could facilitate micturition. Indeed, administration of clonidine stimulates bladder motility in cats by depressing sympathetic outflow to the bladder [7].

References

1. Walts LF, Kauffman RD, Moreland JR, Weiskopf M. Total hip arthroplasty. An investigation of factors related to postoperative urinary retention. *Clinical Orthopaedics and Related Research* 1985; **194**: 280–282.
2. Stenseth R, Sellevold O, Breivik H. Epidural morphine for postoperative pain experience with 1085 patients. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 148–156.
3. Filos KS, Goudas LC, Patroni O, Polyzou V. Hemodynamic ana analgesic profile after intrathecal clonidine in humans. *Anesthesiology* 1994; **81**: 591–601.
4. Korinek AM, Languille M, Bonnet F, Thibonnier M, Sasano P, Lienhart A, Viars P. Effect of postoperative extradural morphine on ADH secretion. *British Journal of Anaesthesia* 1985; **57**: 407–411.
5. Hamaya Y, Nishikawa T, Dohi S. Diuretic effect of clonidine durig isoflurane, nitrous oxide, and oxygen anesthesia. *Anesthesiology* 1994; **81**: 811–819.
6. Rawal N, Mollefors K, Axelsson K, Lingard RG, Widman B. An experimental study of urodynamic effects of epidural morphine and of naloxone reversal. *Anesthesia and Analgesia* 1983; **62**: 641–647.
7. Krier J, Thor KB, De Groat WC. Effects of clonidine on the lumbar sympathetic pathways to the large intestine and urinary bladder of the cat. *European Journal of Clinical Pharmacology* 1979; **59**: 47–53.

British Journal of Anaesthesia 1996; **76**: 874–876

Removal of the laryngeal mask airway in children: anaesthetized compared with awake

A. J. KITCHING, A. R. WALPOLE AND C. E. BLOGG

Summary

We studied 60 children, aged 12 months to 8 yr, undergoing plastic surgery under general anaesthesia supplemented by regional anaesthesia. Patients were allocated randomly to have the laryngeal mask airway removed either on awakening or while anaesthetized. Subsequent observation of respiratory factors and oxygen saturation showed a significant difference between the groups for coughing ($P < 0.001$), with a greater incidence (17 of 33) in the awake group compared with those from whom the laryngeal mask airway was removed while anaesthetized (two of 27). There were no differences in the incidences of laryngospasm, desaturation ($< 95\%$) and excess salivation between the groups. Removed of the laryngeal mask airway during deep anaesthesia reduced coughing in the immediate postoperative period. (*Br. J. Anaesth.* 1996; **76**: 874–876)

Key words
Anaesthesia, paediatric. Equipment, masks anaesthesia. Children.

The laryngeal mask airway (LMA) has been used for more than 4 yr in children [1] and appears to be associated with fewer respiratory effects compared with tracheal tubes. The designer of the LMA suggested originally [2] that it should be left in place until the patient regained protective airway reflexes; however, the LMA was not used in children at that time. We found that many of our colleagues did not follow the example of Mason and Bingham [1], who left the device *in situ* "until the return of laryngeal reflexes" (particularly in children), for fear of provoking coughing or laryngospasm and desaturation.

There is no objective evidence to suggest that removing the LMA in the conventional manner [2] is better than removing it at a deep plane of anaesthesia. However, two studies in children showed that extubation of conventional tracheal tubes [3, 4] at a deep plane of anaesthesia, rather than with the subject awake, may result in fewer episodes of coughing and arterial oxygen desaturation.

In this study we compared the incidence and severity of adverse respiratory events during the immediate postoperative period in children after removal of the LMA, either under surgical anaesthesia, or on awakening.

Methods and results

A letter was sent to the parents before admission, inviting their child's participation in a randomized, prospective, single-blind study of patients aged 12 months to 8 yr undergoing elective urogenital or lower limb plastic surgery for which general anaesthesia combined with regional block was appropriate. Local Ethics Committee approval was obtained. On admission, written informed consent was obtained from the parents after personal interview. Exclusion criteria were: anaesthesia within 3 months, current or chronic upper airway disease, asthma and congenital heart disease.

Premedication was with oral diazepam 0.3 mg kg^{-1} and oral atropine 30 μg kg^{-1} [5], 1–2 h before operation. Anaesthesia was induced with halothane, oxygen and nitrous oxide (with the parents invited to be present), followed by fentanyl 1 μg kg^{-1} i.v. and insertion of the LMA. Any difficulties in insertion were noted. A rolled-up gauze swab served as a bite block until the LMA was removed. Caudal 0.25% plain bupivacaine was then given in a volume of 0.5 ml kg^{-1} in the majority of cases. Anaesthesia was maintained with appropriate concentrations of oxygen, nitrous oxide and halothane. Oxygen saturation was maintained at or above 95% during operation. Morphine 0.1 mg kg^{-1} i.m. was given when spontaneous ventilation was judged to be satisfactory.

Five minutes before the anticipated end of surgery, anaesthesia was deepened by giving twice the minimum alveolar concentration (MAC) of halothane (adjusted for age) [6] with nitrous oxide. The child was then allocated randomly, by tossing a coin, to have the LMA removed (and replaced with a Guedel airway) (deep group) or left *in situ* (awake group). Each child was then turned onto the left side and transferred to the recovery room, breathing air supplemented by oxygen 4 litre min^{-1} by Hudson's face mask. Diclofenac 12.5 mg (or 25 mg if the child weighed more than 20 kg) was inserted *per rectum* on

---

A. J. KITCHING*, MB, CHB, FRCA, A. R. WALPOLE†, MB, BS, FANZCA, C. E. BLOGG, MB, BS, FRCA, Nuffield Department of Anaesthetics, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE.
Accepted for publication: January 16, 1996.
Present addresses:
*Featherstone Department of Anaesthetics and Intensive Care, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH.
†Anaesthetics Department, Royal Melbourne Hospital, Grattan Street, Parkville 3052, Victoria, Australia.
Correspondence to C.E.B.

Table 1 Observations and management

Laryngospasm	
None	
Mild	Only oxygen required
Severe	Anaesthetist intervention
Coughing	Any episodes in recovery period
Salivation	
None	
Salivation requiring suction	

Table 2 Number of patients with airway complications. ***$P < 0.001$ between groups (chi-square)

	Group D (deep) ($n = 27$)	Group A (awake) ($n = 33$)
Complication		
$Sp_{O_2} < 95\%$	5	12
Laryngospasm		
None	16	22
Mild	8	10
Severe	3	1
Coughing	2	17***
Excess salivation (requiring suction)	1	5

arrival in the recovery room. A pulse oximeter probe (Ohmeda 3700) was applied to a finger of the uppermost hand and haemoglobin oxygen saturation and heart rate were displayed. Continuous close observation by one of the investigators and routine observations by trained nursing staff were made of coughing, laryngospasm, airway obstruction, changes in oxygen saturation and heart rate, for 60 min from the end of anaesthesia or until the child was awake (whichever was sooner). Observations and management were recorded (table 1). The LMA or Guedel airway was removed in the recovery room when the child awoke sufficiently to swallow.

Heart rate and oxygen saturation (Sp_{O_2}) from the pulse oximetry were stored on computer for further analysis (Polysomnography program, K. R. Casey).

We studied 60 children; 59 were boys undergoing plastic surgery on the urogenital system; there was one girl undergoing removal of a thigh haemangioma who was allocated randomly to the deep group. In 27 patients the LMA was inserted at a deep plane of anaesthesia (group D) and in 33 when they awoke (group A).

The mean weight of patients in the deep group (D) was 14.7 kg compared with 13.4 kg in the light group (A). The mean age of patients in group D was 30.93 months and 25.3 months in group A.

The number of patients with airway complications in each group is shown in table 2. Neither patient in the deep group who coughed had oxygen saturation values less than 95%. However, four of 17 patients who coughed in the awake group had saturation values of 95% or less during the coughing episodes. Four of those in the awake group who coughed did so within the 5 min before its removal and nine coughed at the time of removal. None in this group required a Guedel airway. Values of oxygen saturation were regarded as reliable if the pulse waveform was regular and corresponded to that displayed on the electrocardiogram.

Patient data were compared using Student's *t* test, while categorical data were compared using the chi-square test with Yates' correction, $n \times 2$ contingency test or Fisher's exact test. $P < 0.05$ was considered significant.

There were no significant differences between the groups in age, weight, salivation, stridor or incidence and severity of desaturation. The only complication that was significant was an increase in the incidence of coughing in the awake group in the recovery period. In four of 17 patients who coughed, saturation decreased to 95% or less.

Comment

We conducted a randomized, prospective study to compare the incidence of airway complications in young children (aged 1–8 yr) after removal of the LMA at either a deep plane of anaesthesia or when the child was awake.

We used a standard anaesthetic regimen so that the groups were as comparable as possible. I.v. induction agents were not used because we knew that in some of these children it would be difficult to obtain venous access and inhalation induction would be more appropriate. We therefore decided from the outset to use halothane and nitrous oxide for induction of anaesthesia in all patients. Further, thiopentone and propofol, our i.v. induction agents of choice, are known to have different effects on airway excitability.

When the child was anaesthetized we used a small dose of i.v. fentanyl to suppress airway reflexes in all patients before insertion of the LMA. A caudal extradural block or alternative block provided analgesia for the operative site, and all patients received a small dose of morphine 0.1 mg kg^{-1} i.m. during operation. Thus we eliminated airway irritability caused by pain of the operation site, and therefore airway complications were likely to be secondary to the local effect of the LMA.

Failure to prevent coughing in the recovery period can be a problem after plastic surgery operations: the induced increase in venous pressure can lead to oozing from the wound edge, and even haematoma formation, which could impair the viability of tissue flaps and grafts.

Therefore, for older infants and young children we now advocate removal of the LMA at a deep plane of anaesthesia to remove the stimulating effect on the airway. This supports the results of other studies [3, 4] comparing deep *vs* awake extubation of tracheal tubes which demonstrated a difference in saturation between the two groups, with better outcome in the deep group.

Acknowledgement

We thank Drs J. W. Sear and J. D. Young for statistical advice and Sister Iris Holmes and recovery room nursing staff for their support.

References

1. Mason DG, Bingham RM. The laryngeal mask airway in children. *Anaesthesia* 1990; 45: 760–763.

2. Brain AIJ. The laryngeal mask—a new concept in airway management. *British Journal of Anaesthsia* 1983; 55: 801–805.
3. Patel RI, Hannallah RS, Norden J, Casey WF, Verghese ST. Emergence airway complications in children: a comparison of tracheal extubation in awake and deeply anesthetised patients. *Anesthesia and Analgesia* 1991; 73: 266–270.
4. Pounder DR, Blackstock D, Steward DJ. Tracheal extubation in children: halothane versus isoflurane, anesthetized versus awake. *Anesthesiology* 1991; 74: 653–655.
5. Omokui S. *The Anesthesia Drug Handbook*. St Louis: Mosby Year Book, 1992; 13.
6. Gregory CA, Eger EI, Munson E. The relationship between age and halothane requirement in man. *Anesthesiology* 1969; 30: 488–491.

British Journal of Anaesthesia 1996; **76**: 877–878

CASE REPORTS

Fracture of the cricoid cartilage after Sellick's manoeuvre

K. J. HEATH, M. PALMER AND S. J. FLETCHER

Summary

We report a case of fracture of the cricoid cartilage associated with cricoid pressure during rapid sequence tracheal intubation in a patient with status asthmaticus. This patient had a history of laryngeal trauma 48 yr previously. Fracture of the cricoid cartilage has not been reported previously after cricoid pressure. (*Br. J. Anaesth.* 1996; **76**: 877–878)

Key words

Larynx, cricoid pressure. Complications, fractured cricoid cartilage.

Case report

A 67-yr-old man was admitted to hospital suffering from acute exacerbation of bronchial asthma. He had a long-standing history of asthma and chronic obstructive airways disease and had been treated with bronchodilators and inhaled steroids for many years.

He had been in hospital for 48 h when his condition worsened and he became progressively hypoxic and hypercapnic, despite nebulized salbutamol therapy; he developed a "silent" chest with arterial blood–gas tensions of Pa_{CO_2} 15 kPa and Pa_{O_2} 8.5 kPa on an inspired oxygen fraction of 0.6. The decision was made to perform tracheal intubation and intermittent positive pressure ventilation. He was transferred to the intensive therapy unit and tracheal intubation was carried out by an anaesthetic senior registrar using ketamine 1 mg kg^{-1} and suxamethonium 1 mg kg^{-1}, with an experienced operating department assistant (ODA) performing cricoid pressure. Intubation was easy, with a grade 1 [1] view of the larynx, and a size 9 cuffed oral tracheal tube was passed. The patient underwent intermittent positive pressure ventilation requiring inflation pressures of up to 35 cm H_2O, and was treated with bronchodilators and hydrocortisone. A chest radiograph performed shortly after tracheal intubation revealed slightly hyperinflated lungs and the tracheal tube in a satisfactory position; there were no other abnormalities on the chest radiograph.

The patient made a rapid recovery and 24 h later was assessed as being ready for extubation. Almost immediately after extubation the patient developed marked inspiratory stridor, severe hypoxia and suffered a brief cardiorespiratory arrest. His trachea was re-intubated rapidly by an anaesthetic senior house officer and cricoid pressure was applied by an experienced intensive care nurse. On this occasion the larynx was difficult to see initially; however, a good view of the vocal cords was obtained by repositioning the patient's head. The laryngeal structures were noted to be swollen but not markedly, a size 9 cuffed oral tracheal tube was reinserted and the lungs ventilated again, requiring inflation pressures of 30–36 cm H_2O. Another chest radiograph was obtained shortly after re-intubation; this showed a possible mediastinal mass that could have accounted for the marked stridor after extubation. The tracheal tube was noted to be in a satisfactory position, level with the fifth thoracic vertebra, and there were no signs of barotrauma or surgical emphysema to account for the patient's difficulty in breathing.

The patient was investigated further for a mediastinal mass because he was noted to have generalized swelling of his neck and dilatation of the veins of his chest and upper extremities, consistent with a possible diagnosis of superior vena cava obstruction. It was suggested that a mediastinal mass could have accounted for the marked inspiratory stridor immediately after extubation and the clinical signs. A limited CT scan of the patient's upper mediastinum, however, showed no abnormalities and when the chest radiograph was reviewed by a consultant radiologist it was reported to show some increased shadowing at the left lung base, but no other abnormal findings. Fibreoptic bronchoscopy was also performed which showed a normal tracheobronchial tree, the larynx was not examined fibreoptically as the tracheal tube was positioned below the larynx and it was not felt necessary to withdraw the tube to examine the larynx.

It was difficult to wean the patient from the ventilator and he underwent a formal tracheotomy performed by an ENT senior registrar on day 8 after admission to the intensive care unit. At operation the surgeon reported that the cricoid cartilage was partially calcified and that there was an undisplaced fracture to the left of the midline of the cricoid arch. The surgeon suggested that the fracture may have been caused by cricoid pressure.

The patient made a slow recovery from his asthma attack and was eventually discharged to the ward breathing spontaneously through his tracheostomy. When the patient had recovered sufficiently to provide a full history, he denied any recent trauma;

K. J. HEATH, MS, BS, BSC, DMCC, FRCA, M. PALMER, MB, BS, S. J. FLETCHER, MB, BS, FRCA, Anaesthetic Department, Norfolk and Norwich Hospital, Brunswick Road, Norwich, Norfolk NR1 3SR. Accepted for publication: January 22, 1996.

however, on further questioning he admitted that he had been in hospital when aged 19 yr after an accident where he had managed to partially hang himself. He had also sustained direct blunt trauma to his larynx 20 yr previously during a caravaning accident but had not been hospitalized on that occasion.

We suggest that the fracture of this patient's cricoid cartilage may have been caused by Sellick's manoeuvre in the presence of a weakened cricoid cartilage associated with the hanging accident when the patient was 19 yr of age and possibly with later more minor laryngeal trauma. This patient's long-term steroid therapy may also have caused some weakening of the cricoid cartilage. Inspiratory stridor after extubation could have been caused by either oedema associated with fracture of the cricoid cartilage or collapse of the fractured cricoid cartilage inwards on inspiration. The other possible causes for stridor after extubation were excluded, such as a mediastinal mass or surgical emphysema associated either with the fractured cricoid cartilage or barotrauma from high airway pressures.

Discussion

Cricoid pressure was first described by Sellick in 1961 [2]. It is often difficult to judge exactly how much pressure to exert during Sellick's manoeuvre. Sellick referred to "firm" pressure in his original article [2] and "the pressure which would cause pain if applied to the bridge of the nose" has also been suggested [3]. A force of 44 N [4] applied to the cricoid ring pressing back against the bodies of the cervical vertebrae has been shown to be effective in protecting the majority of adult patients from regurgitation of gastric contents.

There are several potential complications associated with cricoid pressure, such as rupture of the oesophagus should vomiting occur during the manoeuvre or aggravation of cervical spine injury. Incorrectly applied cricoid pressure can distort the view of the larynx making tracheal intubation difficult. Complete airway obstruction has been caused by Sellick's manoeuvre [5] in a patient undergoing rapid sequence induction of anaesthesia with an undiagnosed lingual thyroid that resulted in supraglottic obstruction when cricoid pressure was applied. There has also been a case of airway obstruction after cricoid pressure in a patient with undiagnosed traumatic injury [6]. In this case the laryngeal injury was acute and the resulting airway obstruction required urgent surgery.

Our case is unique in that the patient underwent tracheal intubation for medical reasons and there was no acute trauma to the larynx. Intubation was carried out by a senior anaesthetist with an experienced assistant in order to minimize any complications, with what was essentially an emergency procedure in a patient *in extremis*; it would have been unlikely in these circumstances that cricoid pressure would have been applied incorrectly. It has been demonstrated, however, that there is a wide variation in force applied to the cricoid ring during cricoid pressure, even by experienced staff. Pressures applied have ranged from 10.8 to 120.6 N [7]. Laryngotracheal injury is rare, requiring considerable force. It would be highly unlikely, even if cricoid pressure was applied too forcibly, that a fracture could occur in a normal cricoid cartilage. Eighty percent of laryngeal injuries and 90 % of fractures, dislocations and separation of the laryngotracheal skeleton are caused by significant, high velocity blunt trauma sustained during road traffic accidents [8]. These high velocity injuries are often associated with multisystem trauma and cervical spine injury. Fracture of the thyroid cartilage is the most frequently encountered injury to the larynx, while fracture of the cricoid alone is unusual; in most cases fractures of the cricoid cartilage also involve the trachea or the thyroid cartilage. Underlying weakness of the cricoid ring was therefore highly likely in our patient.

Hanging is the other main recognized cause of laryngeal trauma [9], and we suggest that our patient had a weakened cricoid cartilage or even an ununited fracture as a result of his hanging injury at 19 yr of age. In a series of 80 consecutive cases of death caused by hanging, 45 % were associated with laryngeal trauma. In this series, however [9], the cricoid cartilage was never fractured and there were no fractures of the larynx in subjects less than 25 yr of age. The second injury to this patient's neck occurred 20 yr ago, but did not result in hospital admission; as significant force is required to fracture the cricoid cartilage it is unlikely that the cricoid ring was fractured at that time. We postulate, therefore, that the old injuries to this patient's larynx together with long-term steroid therapy caused weakening that resulted in fracture of the cricoid cartilage when routine cricoid pressure was applied during rapid sequence tracheal intubation for status asthmaticus.

References

1. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; **39**: 1105–1111.
2. Sellick BA. Cricoid pressure to control regurgitation of stomach contents during induction of anaesthesia. *Lancet* 1961; **2**: 404–406.
3. Mehrotra D, Paust JC. Antacids and cricoid pressure in prevention of fatal aspiration syndrome. *Lancet* 1979; **2**: 582–583.
4. Wraight WJ, Chamney AR, Howells TH. The determination of an effective cricoid pressure. *Anaesthesia* 1983; **38**: 461–466.
5. Georgescu A, Miler JN, Lecklitner ML. The Sellick manoeuvre causing complete airway obstruction. *Anesthesia and Analgesia* 1992; **74**: 457–459.
6. Shorten GD, Alfille PH, Gliklich RE. Airway obstruction following application of cricoid pressure. *Journal of Clinical Anaesthesia* 1991; **3**: 403–405.
7. Howells TH, Chamney AR, Wraight WJ, Simons RS. The application of cricoid pressure. An assessment and a survey of its practice. *Anaesthesia* 1983; **38**: 457–460.
8. Colombo E, Murruni G. Etiopathogenesis and biodynamics of closed laryngo-tracheal injuries. *Acta Otorhinolaryngologica Italica* 1989; (Suppl. 26): 1–14.
9. Simonsen J. Patho-anatomic findings in neck structures in asphyxiation due to hanging: a survey of 80 cases. *Forensic Science International* 1988; **38**: 83–91.

British Journal of Anaesthesia 1996; **76**: 879–880

Balloon mitral valve dilatation as an aid to weaning from ventilatory support in patients with intractable pulmonary oedema caused by severe mitral stenosis

G. DAVIS, R. M. KHAN, N. RANDALL, J. S. WRIGHT AND D. H. ROBERTS

Summary

Intractable pulmonary oedema in patients undergoing mechanical ventilation must be investigated as older patients with severe mitral stenosis can be rescued by balloon dilatation of the mitral valve, thus enabling elective cardiac surgery at reduced risk. We describe two such cases and discuss the role of transoesophageal echocardiography in the intensive care unit in the diagnosis and management of these patients. (*Br. J. Anaesth.* 1996; **76**: 879–880)

Key words

Complications, pulmonary oedema. Complications, stenosis. Monitoring, echocardiography.

Mechanical ventilation is often used to rescue patients who have respiratory arrest caused by severe pulmonary oedema. We report two patients in whom repeated attempts at weaning from ventilatory and haemodynamic support were unsuccessful because of severe mitral stenosis. The success of emergency balloon dilatation of the mitral valve in the management of this problem is discussed.

Case reports

PATIENT NO. 1

A 61-yr-old male in atrial fibrillation underwent elective cardiac catheterization for severe mitral stenosis (estimated valve area on echocardiography of 0.9 cm^2). He was found to have severe pulmonary hypertension and significant two-vessel coronary artery disease with moderate left ventricular function. He developed severe pulmonary oedema leading to respiratory arrest 4 h later and required mechanical ventilation. He became severely hypotensive (systolic arterial pressure 75 mm Hg) requiring treatment with i.v. dobutamine, dopamine and noradrenaline. He continued to suffer from pulmonary oedema.

Transoesophageal echocardiography (fig. 1) showed severe mitral stenosis with calcification of the anterior mitral valve leaflet, mild mitral regurgitation and absence of thrombus in the left atrium and atrial appendage. He therefore underwent emergency Inoue balloon percutaneous transvenous mitral commissurotomy (PTMC) up to a maximum dilatation of 26 mm. There was an immediate decrease in mitral valve end-diastolic gradient from 12 to 5 mm Hg and echocardiographically derived mitral valve area increased to 1.7 cm^2. Echo-Doppler however, showed increased mitral regurgitation. Despite this he was weaned successfully from ventilatory and inotrope support within 3 days and was discharged home 4 days later. He underwent successful elective mitral valve replacement and coronary artery bypass surgery 2 months after PTMC.

PATIENT NO. 2

A 59-yr-old female with known mitral stenosis and cerebrovascular disease presented as an emergency in an unresponsive state with severe pulmonary oedema requiring ventilation. She was profoundly hypotensive with a systolic arterial pressure of 60 mm Hg which required maximum inotropic support. Multiple attempts at ventilatory weaning were however, unsuccessful because of persistent pulmonary oedema. Transoesophageal echocardiography (fig. 1) showed the mitral valve to be tightly stenosed with a mobile anterior leaflet but an immobile calcified posterior leaflet with thickening and calcification of the subvalvar apparatus. There was mild mitral regurgitation. The left atrium was dilated with spontaneous contrast but no thrombus. She underwent emergency Inoue balloon PTMC and was weaned successfully from ventilatory support within 24 h. An increase in echocardiographically derived mitral valve area (0.7 to 1.9 cm^2) was achieved but there was now moderate mitral regurgitation. Her symptoms remained improved at outpatient follow-up 3 months later, but elective mitral valve replacement is being considered.

Discussion

The presence of severe pulmonary oedema does not necessarily imply a diagnosis of "left ventricular failure" and echocardiography should be performed

---

G. DAVIS, MRCP, R. M. KHAN, FRCS, J. S. WRIGHT, FRCP, D. H. ROBERTS, MD, MRCP (Regional Cardiothoracic Centre); N. RANDALL, BM, FRCA (Department of Anaesthetics); Blackpool Victoria Hospital, Blackpool FY3 8NR. Accepted for publication: February 7, 1996.

Correspondence to G.D.

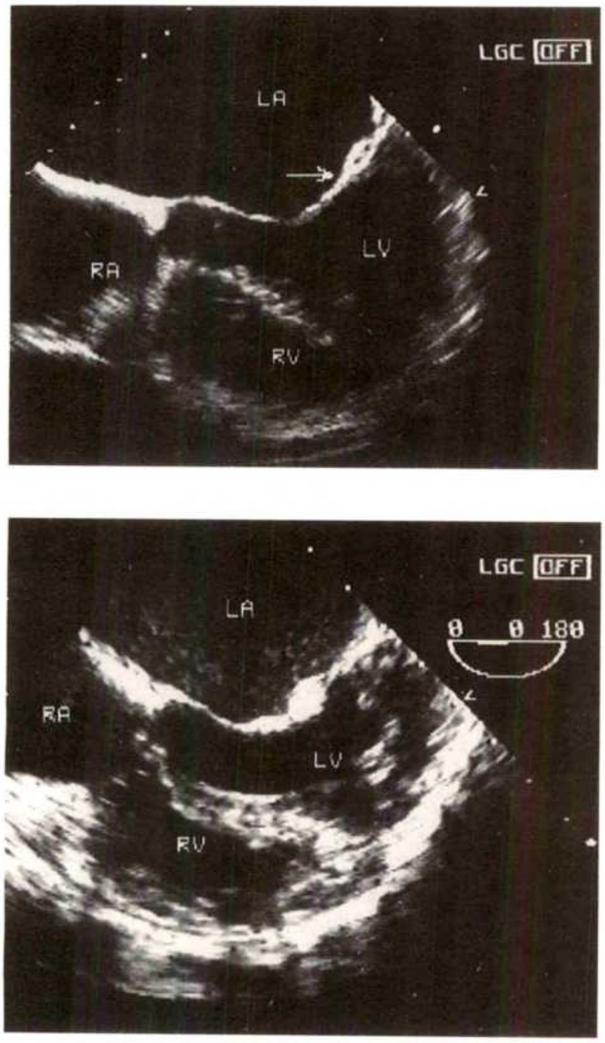


Figure 1 Four-chamber transoesophageal echocardiographic images in patient No. 1 (top) and patient No. 2 (bottom). On both images there is dilatation and a hazy appearance (spontaneous contrast with increased risk of clot formation) of the left atrium. The mitral valve leaflets (arrow, top) are thickened and calcified with restricted opening on both images. RA = Right atrium, RV = right ventricle, LV = left ventricle, LA = left atrium.

to exclude mitral stenosis as a cause of intractable pulmonary oedema in patients undergoing ventilation. Mitral valve replacement in such patients carries prohibitive risks which are increased further in the presence of significant coronary artery disease [1].

Although closed mitral valvotomy and PTMC are equally effective in providing haemodynamic improvement in selected patients with severe mitral stenosis, PTMC may do so more cost effectively and without increased complications [2]. Wilkins and colleagues [3] have suggested an echocardiographic scoring system to predict the result of balloon dilatation and have shown that short-term outcome is related directly to the degree of valve leaflet thickening and involvement of the subvalvar apparatus (thickening and calcification). Transoesophageal echocardiographic examination is also important before PTMC to detect the presence of left atrial thrombus [4] which is a relative contraindication to balloon intervention. This is more likely to be present in older patients with left atrial dilatation and atrial fibrillation.

Inoue balloon PTMC has been shown previously to be particularly useful in treating intractable heart failure caused by severe mitral stenosis in pregnant patients [5] and in critically ill young patients [6]. We suggest that this procedure is also useful in older critically ill patients, even with mitral valves with less than ideal characteristics, as a means of achieving a better cardiac haemodynamic state, thus enabling weaning from ventilatory support and allowing elective mitral valve replacement if indicated on symptomatic grounds.

References

1. Jones EL, Weintraub WS, Craver JM, Guyton RA, Shen Y. Interaction of age and coronary disease after valve replacement: implications for valve selection. *Annals of Thoracic Surgery* 1994; **58**: 378–384.
2. Turi ZG, Reyes VP, Raju BS, Raju AR, Kumar DN, Rajagopal PR, Sathyanarayana PV, Rao DP, Srinath K, Peters P, Connors B, Fromm B, Farkas P, Wynne J. Percutaneous balloon versus surgical closed commissurotomy for mitral stenosis. A prospective randomized trial. *Circulation* 1991; **83**: 1179–1185.
3. Wilkins GT, Weyman HF, Abascal VM, Block PC, Palicous IF. Percutaneous balloon dilation of the mitral valve: an analysis of the echocardiographic variables related to outcome and the mechanism of dilatation. *British Heart Journal* 1988; **60**: 299–308.
4. Thomas MR, Monaghan MJ, Smyth DW, Metcalfe JM, Jewitt DE. Comparative value of transthoracic and transoesophageal echocardiography before balloon dilatation of the mitral valve. *British Heart Journal* 1992; **68**: 493–497.
5. Kalra GS, Arora R, Khan JA, Nigam M, Khalillulah M. Percutaneous mitral commissurotomy for severe mitral stenosis during pregnancy. *Catheterization and Cardiovascular Diagnosis* 1994; **33**: 28–30.
6. Patel JJ, Munclinger MJ, Mitha AS, Patel N. Percutaneous balloon dilatation of the mitral valve in critically ill young patients with intractable heart failure. *British Heart Journal* 1995; **73**: 555–558.

British Journal of Anaesthesia 1996; **76**: 881–890

CORRESPONDENCE

Suxamethonium and auditory evoked potentials

Sir,—I read with interest the article by Brunner and colleagues on the relationship between suxamethonium and cortical auditory evoked potentials [1]. The focus of the article was the hypothesis that suxamethonium may cause arousal of anaesthetized patients, but no plausible explanations were offered by the authors as to the possible mechanism. I suspect that the authors overlooked the effects of neuromuscular blockers on the muscles of the tympanum (tensor tympani and stapedius) which are the most sensitive muscles in the body to the action of blocking drugs. For example, there is considerable literature on the early diagnosis of myasthenia gravis by testing the reflex tensioning of the middle ear ossicles with impedance techniques.

Thus the effect of suxamethonium on the auditory evoked response may not be concerned with arousal. Instead it may merely be the result of abolishing the tensioning reflex mediated by the stapedius, allowing a much larger mechanical signal through to the inner ear and therefore causing a larger stimulus up the auditory nerve. The authors even cited a reference reporting the absence of the "arousal" effect of suxamethonium in the presence of previous non-depolarizing paralysis (ref. [10]) which is what one would expect: when the stapedius has been blocked totally, it cannot be blocked further. The results of this article are nevertheless interesting. The discussion section, however, might perhaps have been reduced to a single 10-line paragraph had the authors taken into account the physiology of the stapedius reflex.

J. Ponte
King's College Hospital
London

1. Brunner MD, Nathwani D, Rich PA, Thornton C, Doré CJ. Effect of suxamethonium on the auditory evoked response in humans. *British Journal of Anaesthesia* 1996; **76**: 34–37.

Sir,–Our study showed that suxamethonium had an arousal effect according to the auditory evoked response (AER). In the discussion section of our article, we outlined the possible causes of this effect and, according to the literature, felt that cortical stimulation secondary to increased muscle spindle activity after muscle fasciculation or direct spindle stimulation by suxamethonium itself, may be responsible for the arousal pattern which we observed.

Theoretically, as Dr Ponte points out, paralysis of the stapedius by suxamethonium could increase the input up the auditory nerve resulting in an AER response similar to that seen with arousal. However, if this were so, all neuromuscular blocking drugs would have an arousal effect on the AER. There is currently no evidence in the literature to support this theory. In fact, in an article published recently in this journal [1], Richmond and colleagues showed that vecuronium had no effect on the AER.

Regarding the article by Mori, Iwabuchi and Fujita [2], Dr Ponte is correct in saying that these authors found that suxamethonium failed to cause arousal in the presence of previous non-depolarizing paralysis. However, the authors also found that non-depolarizing drugs failed to cause arousal, which they should have if the stapedius reflex were a factor. On the other hand, their findings support our assertion that arousal after suxamethonium may result from muscle spindle stimulation, because its effect on the EEG can be blocked by non-depolarizing blockers which prevent fasciculation. Also, Mori and colleagues did not measure the AER in their subjects. They examined instead EEG responses where auditory reflexes are less important.

M. D. Brunner
C. Thornton
D. E. F. Newton
Northwick Park Hospital
Harrow, Middlesex

1. Richmond CE, Matson A, Thornton C, Doré CJ, Newton DEF. Effect of neuromuscular block on depth of anaesthesia as measured by the auditory evoked response. *British Journal of Anaesthesia* 1996; **76**: 446–448.
2. Mori K, Iwabuchi K, Fujita M. The effects of depolarizing muscle relaxants on the electroencephalogram and the circulation during halothane anaesthesia in man. *British Journal of Anaesthesia* 1973; **45**: 604–610.

Extradural clonidine for postoperative pain relief

Sir,—With regard to a recent letter by Nishikawa [1] criticizing pain assessment by Lee and Rubin [2], we feel that, as our recent article [3] used similar methodology to theirs, we should reply to the points raised.

First, Nishikawa questions that objective assessment of pain is possible in small children. This is an area of obvious difficulty and is the reason why a previously validated [4] objective pain scoring system was used in both studies [2, 3]. This was used by staff [2] or parents [3] to decide when analgesia was necessary. Quite how this makes bias "likely" when observations of randomized groups are being made double-blind is unclear to us.

Nishikawa also states that he "cannot exclude…that intense sedation induced by extradural clonidine (with local anaesthetics) would make estimation of pain intensity impossible". He cites his own study [5] in support of this. However, this article makes no attempt to assess pain in its methodology. In addition, all patients were adults who were premedicated and sedated during operation. Despite this, and one group receiving a larger mean dose of clonidine (3.3 μg kg^{-1}) than in the paediatric studies (2 μg kg^{-1}), none was "sedated to the degree that she could not respond to verbal commands". This suggests that ability to communicate was retained.

Lee and Rubin [2] found it difficult to separate analgesia and sedation in their patients receiving extradural clonidine. They also used sedative premedication. In our study [3] no premedication was used and we confirmed that clonidine 2 μg kg^{-1} provided a longer duration of analgesia than adrenaline 1:200000 when added to caudal 0.25% bupivacaine 1 ml kg^{-1} (medians: clonidine 5.8 h, adrenaline 3.2 h; $P < 0.05$). There was no difference in time to spontaneous eye opening after cessation of anaesthesia (medians: clonidine 21 min, adrenaline 20 min) or sedation scores at 4 h (medians: clonidine 0, adrenaline 0). Only three patients in the clonidine group (total 20) required analgesia at 4 h when median sedation score was 0 (eyes open spontaneously). Therefore, it is our contention that sedation does not preclude estimation of pain in children given extradural clonidine 2 μg kg^{-1} in combination with local anaesthetic, but that the use of other sedative drugs may introduce this difficulty.

B. Cook
E. Doyle
Department of Anaesthesia
Royal Infirmary of Edinburgh
Edinburgh

1. Nishikawa T. Extradural clonidine for postoperative pain relief. *British Journal of Anaesthesia* 1996; **76**: 171.
2. Lee JJ, Rubin AP. Comparison of a bupivacaine–clonidine mixture with plain bupivacaine for caudal analgesia in children. *British Journal of Anaesthesia* 1994; **74**: 258–262.
3. Cook B, Grubb DJ, Aldridge LA, Doyle E. Comparison of the effects of adrenaline, clonidine and ketamine on the duration of caudal analgesia produced by bupivacaine in children. *British Journal of Anaesthesia* 1995; **75**: 698–701.
4. Hanallah RS, Broadman LS, Belman AB, Abramowitz MD, Epstein BS. Comparison of caudal and ilioinguinal nerve blocks for control of post-orchidopexy pain in pediatric ambulatory surgery. *Anesthesiology* 1987; **66**: 832–834.
5. Nishikawa T, Dohi S. Clinical evaluation of clonidine added to lidocaine solution for epidural anesthesia. *Anesthesiology* 1990; **73**: 853–859.

Sir,—I read with interest the article by Cook and colleagues [1] insisting that sedation does not preclude postoperative pain assessment in small children receiving extradural clonidine and local anaesthetic. I cannot wholly agree with their contention. First, I think that the pain scoring system [2] used in their study did not necessarily provide real assessment of postoperative pain intensity, because estimation of pain with this method is likely to be affected by other discomforts (for example, sleep, hunger or thirst, etc.). Second, paediatric patients received analgesics only when the parent judged its requirements in their study. Therefore, some bias caused by individual variability in the parent's care may be introduced in the quantitative assessment of analgesia.

I still believe that the most objective assessment of postoperative pain can be judged only by the same attending staff, blinded to the treatment, irrespective of patient age, and that it is difficult to separate analgesia from sedation in paediatric patients, as Lee and Rubin [3] found. More importantly, it appears curious to me that Cook and colleagues did not observe significant sedation in patients receiving caudal extradural clonidine 2 $\mu g\ kg^{-1}$ with 0.25% bupivacaine 1 ml kg^{-1} compared with those receiving caudal adrenaline 5 $\mu g\ kg^{-1}$ with 0.25% bupivacaine 1 ml kg^{-1}, as the smaller dose of extradural clonidine of less than 2 $\mu g\ kg^{-1}$ also produced intense sedation in adults in our study [4].

T. NISHIKAWA
Tsukuba, Japan

1. Cook B, Grubb DJ, Aldridge LA, Doyle E. Comparison of the effects of adrenaline, clonidine and ketamine on the duration of caudal analgesia produced by bupivacaine in children. *British Journal of Anaesthesia* 1995; **75**: 698–701.
2. Hannallah RS, Broadman LM, Belman AB, Abramowitz MD, Epstein BS. Comparison of caudal and ilioinguinal/iliohypogastric nerve blocks for control of post-orchiopexy pain in pediatric ambulatory surgery. *Anesthesiology* 1987; **66**: 832–834.
3. Lee JJ, Rubin AP. Comparison of a bupivacaine–clonidine mixture with plain bupivacaine for caudal analgesia in children. *British Journal of Anaesthesia* 1994; **72**: 258–262.
4. Nishikawa T, Dohi S. Clinical evaluation of clonidine added to lidocaine solution for epidural anesthesia. *Anesthesiology* 1990; **73**: 853–859.

Aprotinin during liver transplantation

Sir,—We were interested to read the double-blind, randomized study by Milroy and colleagues [1] on haemodynamic stability after administration of aprotinin during orthotopic liver transplantation (OLT). We wish to make the following observations.

Aprotinin reduces transfusion requirements and blood loss in patients undergoing heart surgery [2]. However, this beneficial effect has never been assessed in patients undergoing OLT. In the reference mentioned by the authors [3], as in all articles published previously, comparisons were made with historical controls. Moreover, aprotinin did not significantly reduce oozing during OLT in the only randomized study [4].

In the introduction to the article, the authors wrote "the aim of the present study was to determine if aprotinin influenced blood loss, blood product requirements...". We were disappointed not to find the answer in the results as they studied 55 patients, a large sample, in a controlled, randomized study, but failed to answer the question: does aprotinin reduce blood loss in OLT?

C. LENTSCHENER
D. BENHAMOU
Département D'Anesthésie-Réanimation
Hôpital Antoine Béclère
Clamart, France

1. Milord JS, Cottam S, Tan KC, Hilmi I, Oyesola B. Improved haemodynamic stability with administration of aprotinin during liver transplantation. *British Journal of Anaesthesia* 1995; **75**: 747–751.
2. Bidstrup BP, Royston D, Sapsford RN, Tauylor KM. Reduction in blood loss and blood use after cardiopulmonary bypass with high dose aprotinin (Trasylol). *Journal of Thoracic and Cardiovascular Surgery* 1989; **97**: 364–372.
3. Grosse H, Lobbes W, Frambach M, Ringe B, Barthels M. Influence of high dose aprotinin on hemostasis and blood requirement in orthotopic liver transplantation. *Seminars in Thrombosis and Hemostasis* 1993; **19**: 302–305.
4. Groh J, Welte M, Azad SC, Forst H, Pratschke E, Kratzer MAA. Does aprotinin affect blood loss in liver transplantation? *Lancet* 1992; **340**: 173.

Sir,—We appreciate the chance to reply to the comments of Drs Lentschener and Benhamou. Blood loss values were omitted from this article. Intraoperative blood loss was higher in the placebo group (median 4676.5 ml (interquartile range 3060–6230 ml)) compared with the aprotinin-treated group (3467.5 (1770–5245) ml). These data were subjected to statistical analysis using non-parametric tests. The differences in intraoperative blood loss between the two groups did not reach statistical significance.

There was also a trend towards reduced blood transfusion requirements during and after operation in the aprotinin-treated group, but again this was not statistically significant.

Even though Lentschener and Benhamou consider that our study was conducted on a large group of patients, in retrospect we are of the opinion that this study did not have sufficient statistical power to either support or refute the question it was designed to answer, namely does aprotinin reduce blood loss during orthotopic liver transplantation (OLT)? We have realized that patient selection may not have been ideal in helping to answer this important question.

Our original approach for this study was to include all suitable patients undergoing OLT for chronic or acute hepatic failure. This led to the inclusion of a high proportion of "low risk" patients (48% in the placebo group and 29% in the aprotinin group) with a preoperative diagnosis of primary biliary cirrhosis and primary sclerosing cholangitis. We now consider these patients to be at low risk of intraoperative fibrinolysis, and no longer administer prophylactic antifibrinolytic therapy.

It was our intention to publish this article merely to highlight the interesting and previously (to our knowledge) unreported finding that administration of aprotinin during OLT can confer statistically significant improvements in haemodynamic stability during the post-reperfusion phase.

We are currently conducting a more powerful randomized, double-blind study in patients we consider to be at high risk of intraoperative fibrinolysis and bleeding during OLT to definitively answer Lentschener and Benhamou's question.

S. COTTAM
S. J. MILROY
Department of Anaesthetics and Liver Transplantation
King's College Hospital, London

Aortic stent surgery

Sir,—We were interested to read the case report by Greiff, Thompson and Langham [1].

To our knowledge there are four centres in the UK, including Leicester, that are involved in endoluminal repair of abdominal aortic aneurysm. At the 1995 annual scientific meeting of the Vascular Surgical Society, the results of several of the centres were presented, and also recently in Sydney [2]. It is interesting to note that the procedure is not always as straightforward as suggested in the case report by Greiff, Thompson and Langham. Failure to deploy the stent is not uncommon [3]. The need to convert to an open operation may occur in up to 35% of patients. Although there is a definite learning curve with mortality being reduced the more experienced the team, perioperative mortality is approximately 10% [4]. Late failure of the graft has also been described.

There are several reasons for these problems. The technique is relatively new and during the early stages of development there is a tendency to use the technique in those patients where open surgery is very likely to result in the death of the patient. For example, the patient may have significant cardiovascular disease and death is a significant risk whatever the operation.

As indicated in the article of Greiff, Thompson and Langham, the main advantage for patients is that when the procedure succeeds smoothly, the postoperative course is usually less complicated than after open surgery. The patient's trachea can usually be extubated early and the patient may be mobilized early. This improved postoperative course may not, however, outweigh the risk of hypotension that occurs while the balloons are inflated to deploy the stent during the procedure. Studies examining the advantages of this technique compared with open surgery in different groups of patients are necessary and also studies evaluating the anaesthetic techniques used.

A. P. BARANOWSKI
M. ADISESHIAH
UCL Hospitals
London

1. Greiff JMC, Thompson MM, Langham BT. Anaesthetic implications of aortic stent surgery. *British Journal of Anaesthesia* 1995; **75**: 779–781.
2. Adiseshiah M, Mcarthy T, Howling S, Lee W, Shaw P. A comparison of intraoperative angiographic estimation with 3-D spiral reconstruction of aortic size for endoluminal repair of abdominal aortic aneurysm. Journal of Endovascular Surgery 1996; 3: 80–81.
3. Chuter TAM, Wendt G, Hopkinson BR, Scott RA, Risberg B, Walker PJ, White G. Transfemoral insertion of a bifurcated endovascular graft for aortic aneurysm repair: the first 22 patients. *Cardiovascular Surgery* 1995; **3**: 121–128.
4. May J, White G, Yu W, Waugh RC, Stephen MS, McGahan T, Harris JP. Endoluminal grafting of aortic aneurysms: causes of failure and their prevention. *Journal of Endovascular Surgery* 1994; **1**: 44–52.

Sir,—We are grateful for the comments of Dr Baranowski and Mr Adiseshiah, and appreciate the opportunity to clarify several points.

Numerous centres within the UK have preliminary experience of this technique, although it is probably true to say that only Leicester and Nottingham have a representative experience. It is certainly true that there is a definite learning curve to this procedure, but we are unaware of any data to support the assertion that mortality is reduced with increasing experience of the team. It is misleading to describe average mortality for this procedure as many of the patients in the larger series are elderly and unfit for routine conventional surgery [1–3].

It is suggested by Dr Baranowski and Mr Adiseshiah that endovascular aneurysm repair be used in those patients where open surgery is likely to result in patient mortality. It is our view that this is precisely the case in which endovascular surgery should be avoided until the learning curve of the procedure has been overcome and conversion to open operation occurs in a low percentage of patients. It is well documented in the literature that conversion during endovascular aneurysm repair results in a high mortality rate. If a failure to deploy the endograft appropriately is occurring in up to 35 % of cases, it may be appropriate to re-think the indications for endovascular repair in this group of patients. At present we feel that a randomized, controlled trial is required to examine procedural morbidity and mortality in patients suitable for both conventional and endovascular aneurysm repair. It must be determined if endovascular aneurysm repair is a safe procedure in "healthy" patients before its use can be advocated routinely in patients unsuitable for conventional transperitoneal surgery.

We were interested to learn that the group at UCL uses significant procedural hypotension during deployment of the aortic stent. During deployment of a balloon expandable stent in our centre, we regard a mean arterial pressure of 70 mm Hg to be adequate.

M. M. THOMPSON
J. GREIFF
Faculty of Medicine
University of Leicester
Leicester

1. May J, White GH, Yu W. Endoluminal grafting of abdominal aortic aneurysms: causes of failure and their prevention. *Journal of Endovascular Surgery* 1994; **1**: 44–52.
2. Marin ML, Veith FJ, Cynamon J. Initial experience with transluminally placed endovascular grafts for the treatment of complex vascular lesions. *Annals of Surgery* 1995; **222**: 449–469.
3. Parodi JC. Endovascular repair of abdominal aortic aneurysms and other arterial lesions. *Journal of Vascular Surgery* 1995; **21**: 549–555.

Suxamethonium in children

Sir,—The importance of recognizing subclinical myopathies in patients undergoing general anaesthesia was demonstrated clearly many years ago [1] and has been stressed recently in the editorial by Hopkins [2].

When the problem of anaesthesia-induced rhabdomyolysis (AIR) is examined retrospectively, a surprising finding is that many clinical reports (including the most recent ones) lack preoperative evaluation of serum creatine kinase (CK) activity. This indicates that our attention to the problem is either poor or frustrated by the knowledge that serum CK activity is not invariably correlated with the presence or absence of myopathic conditions.

The long preclinical phase of many dystrophinopathies, which are frequently involved in AIR [3], may be easily recognized or suspected on the basis of CK activity.

In our experience, a definite *decrease* in postoperative serum CK activity may be expected in the majority of these patients if they receive general anaesthesia without the use of suxamethonium [4]. In rare circumstances, however, a life-threatening AIR may be observed even though suxamethonium has been avoided [5]. Whether or not these accidents define a particular subpopulation of dystrophinopathic patients or a particular pharmaco-metabolic condition caused by general anaesthesia is unknown.

In our opinion, a poorly investigated problem is the metabolic derangement which might occur when the normal activity of the enzyme carnitine-palmitoyl-transferase is simultaneously stressed by increased lipolysis and by anaesthetic agents [6]. Preoperative fasting, anxiety and restlessness could be important in this regard.

F. FIACCHINO
F. CONSONNI
A. DULCAMARA
L. GRANDI
Divisione di Neuroanestesia-Rianimazione
Istituto Neurologico C. Besta
Milano, Italy

1. Bennike KA, Jarnum S. Myoglobinuria with acute renal failure possibly induced by suxamethonium. A case report. *British Journal of Anaesthesia* 1964; **36**: 730–736.
2. Hopkins PM. Use of suxamethonium in children. *British Journal of Anaesthesia* 1995; **75**: 675–677.
3. Farrel PT. Anaesthesia-induced rhabdomyolysis causing cardiac arrest: case report and review of anaesthesia and dystrophinopathies. *Anaesthesia and Intensive Care* 1994; **22**: 597–601.
4. Fiacchino F, Bricchi M, Gemma M, Regi B, Montolivo M, Crippa MT, Ferrazza C, Bruzzone E. Pre- and postoperative serum CK activity in 142 children submitted to "uneventful" anaesthesia for diagnostic muscle biopsy. *Minerva Anestesiologica* 1989; **55**: 11–19.
5. Fiacchino F, Bricchi M, Balestrini MR, Ferrazza C, Montolivo M, Daniel S, Morandi L, Ariano C. Anaesthesiological rhabdomyolysis in muscular dystrophy. *Minerva Anestesiologica* 1984; **50**: 521–526.
6. Zierz S, Schmitt U. Inhibition of carnitine palmitoyl-transferase by malonyl-coA in human muscle is influenced by anesthesia. *Anesthesiology* 1989; **70**: 373.

Sir,—Hopkins' editorial [1] correctly asserts the advantages of suxamethonium but has not detailed the contraindications. There is evidence that it is the dystrophinopathies that account for the unexpected cardiac arrests that occur with suxamethonium [2]. The difficulty in clinical practice is to distinguish the mild, often subclinical, forms of dystrophinopathy, such as Becker's, from normal patients. There may be no family history, and a specific history of muscle cramps with normal exercise, especially in males, may be the only clue to the underlying disorder. Hopkins' observation that cardiac arrest occurred after inhalation induction and suxamethonium is very important, particularly as cardiac arrest has occurred after halothane and isoflurane, without suxamethonium, in patients with dystrophinopathies [3, 4]. On the basis of this evidence I believe the following recommendations can be made: (1) suxamethonium and the volatile anaesthetics are contraindicated in patients with known or suspected dystrophinopathies; (2) the use of suxamethonium should be limited to specific indications, especially in children; and (3) suxamethonium should be avoided after inhalation induction.

Mortality from anaesthesia is very low. A further reduction requires attention to the less frequent but known causes. Adhering to the above guidelines may help.

P. T. Farrell
Department of Anaesthesia and Intensive Care
John Hunter Hospital
Newcastle NSW, Australia

1. Hopkins PM. Use of suxamethonium in children. *British Journal of Anaesthesia* 1995; 75: 675–677.
2. Farrell PT. Anaesthesia-induced rhabdomyolysis causing cardiac arrest: Case report and review of anaesthesia and the dystrophinopathies. *Anaesthesia and Intensive Care* 1994; 22: 597–601.
3. Rubiano R, Chang J-L, Carroll J, Sonbolian N, Larson CE. Acute rhabdomyolysis following halothane anesthesia without succinylcholine. *Anesthesiology* 1987; 67: 856–857.
4. Chalkiadis GA, Branch KG. Cardiac arrest after isoflurane anaesthesia in a patient with Duchenne's muscular dystrophy. *Anaesthesia* 1990; 45: 22–25.

Sir,—Fiacchino and colleagues appear to be advocating routine preoperative screening of creatine kinase (CK) activity and yet they observe that the sensitivity and specificity of this investigation for detecting subclinical myopathies is low. Given that the prevalence of myopathies in the population is low, the predictive value of estimating CK activity renders this an unhelpful screening test. If there are clinical features suggestive of myopathy, or there is a family history of such a condition, CK estimation may form part of the investigative process of the underlying condition, but a normal CK result does not exclude a myopathy and will not, therefore, influence short-term anaesthetic management.

I am sympathetic towards Farrell's views, but before concurring with such rigid and generalized recommendations, it is important to be sure that the necessary alternative techniques are likely to be safer in *all* situations. I believe that first, we should distinguish between those cases where the diagnosis of a myopathy has been made, or seems likely on the basis of clinical information, and those cases where the likelihood of a myopathy is low (no family history or clinical features).

In the former group, it is generally accepted that the incidence and severity of complications attributable to suxamethonium (myotonia, postoperative ventilatory failure [1] and rhabdomyolysis) is so high as to outweigh the potential advantages of suxamethonium. When we consider the choice of maintenance drugs for general anaesthesia in these patients, the situation is not as clear. Hypermetabolic reactions and sudden massive rhabdomyolysis have been reported in dystrophic patients anaesthetized with volatile drugs without suxamethonium, but similar responses can occur in myopathic patients receiving total i.v. anaesthesia [2]. However, I believe that volatile anaesthetics do contribute directly to rhabdomyolysis [3, 4]. These disadvantages of volatile drugs need to be weighed against the detrimental cardiovascular effects of i.v. agents in patients who may have a severe cardiomyopathy. Symptoms of heart failure in patients with Duchenne dystrophy are deceivingly uncommon because of the enforced sedentary existence but myocardial dysfunction is common, as is evident from echocardiographic studies [5], which themselves can fail to detect patients with significant ventricular dysfunction [6]. One should also not ignore that there is, albeit anecdotal, great experience of the safe use of halothane in Duchenne patients.

As I hoped was clear from my editorial [7], the overall incidence of cardiac arrest after suxamethonium is low, but by being meticulous in our preoperative assessment of children it is likely that we can further reduce this incidence. What we cannot quantify are the potential advantages of techniques using suxamethonium. There are no published studies that have adequately compared outcome with these and alternative techniques. Again, as argued in the editorial, such studies would need to be extremely large to achieve sufficient power to detect small, but clinically important differences. Neither are there likely to be published case reports of morbidity or mortality associated with failure to rapidly establish a secure airway when suxamethonium was not used.

There will always be a risk with anaesthesia. For some individuals the risk varies according to the technique/drugs used, but there are many factors that can influence relative risk. It is my view, therefore, that rather than rely on rigid dictates, the anaesthetist must tailor the approach to clinical management to the needs of the individual patient if anaesthetic mortality is to be minimized. This requires anaesthetists to be able physicians, trained to a high level of competence in a range of anaesthetic techniques. It also requires anaesthesia to be a strong academic discipline with practitioners motivated to establish the many strands of evidence required for objective clinical decision making, and with the ability to evaluate these in conjunction with other, often conflicting, priorities. In the absence of firm evidence, clinicians can only guess which approach, in their hands, is most likely to provide the best outcome for the patient: this is what we term "clinical judgement". One aim of my editorial was to highlight that, until we can quantify the complete risk/benefit profile for suxamethonium, its use in children must remain a matter of clinical judgement.

P. M. Hopkins
Academic Unit of Anaesthesia
St James's University Hospital
Leeds

1. Smith CL, Bush GH. Anaesthesia and progressive muscular dystrophy. *British Journal of Anaesthesia* 1985; 57: 1113–1118.
2. Hopkins PM, Ellis FR, Halsall PJ. Hypermetabolism in arthrogryphosis multiplex congenita. *Anaesthesia* 1991; 46: 374–375.
3. Hopkins PM. A quantitative *in vitro* animal model of suxamethonium- and halothane-induced muscle damage. *British Journal of Anaesthesia* 1992; 68: 447P–448P.
4. Hopkins PM. The effects of caffeine and halothane on the $[Ca^{2+}]_i$ of skeletal muscle in the absence and presence of extracellular calcium. *Journal of Physiology (London)* 1993; 459: 14P.
5. Goldberg S, Stern L, Feldman L. Serial two-dimensional echocardiography in Duchenne muscular dystrophy. *Neurology* 1982; 10: 1101–1105.
6. Sethna SF, Rockoff MA, Worthen HM, Rosnow JM. Anesthesia-related complications in children with Duchenne muscular dystrophy. *Anesthesiology* 1988; 68: 462–465.
7. Hopkins PM. Use of suxamethonium in children. *British Journal of Anaesthesia* 1995; 75: 675–677.

Isolated forearm technique

Sir,—In reply to our original letter [1], Healy and Pomfrett [2] chastise us on several counts: that nitrous oxide–oxygen anaesthesia "represents a very specific anaesthetic scenario", that we did not "allay public fears in a public forum" and that the isolated forearm technique (IFT) does not work.

The first implies that nitrous oxide and opioid "anaesthesia" is a little-used, obscure technique, and thus attempts to undermine the significance of the finding that 44% of patients are sufficiently aware to respond to command. Older readers will not need reminding that up until the late 1980s, nitrous oxide–opioid techniques were used commonly in the UK and an MDU anaesthetic adviser was prompted to discourage their use [3]. However, such techniques are still popular in continental Europe [4] and furthermore, studies using these methods continue to appear in reputable anaesthetic journals [5, 6]. Had the IFT been used more widely in the 1980s, British anaesthetists would have been aware much sooner as to how lightly "anaesthetized" their patients were.

With regard to allaying public fears, the authors were interviewed, both individually and together, for various local, national and international radio and regional television networks. During these interviews it was made clear that in the UK today these anaesthetic techniques are used much less commonly than in the past.

The single case of IFT failure [7] which Healy and Pomfrett make so much of occurred during Russell's first study of the IFT when some of the technicalities were still being evaluated, and is only one of many hundreds of successful uses of the procedure. This compares well with technical failure rates of common electronic monitoring devices as a result of poor electrode contact–positioning or diathermy interference.

Healy and Pomfrett suggest that because decerebrate rats show responses to surgical stimuli this invalidates the IFT. Nothing could be further from the truth. The possibility of such subcortical responses in humans is the *sine qua non* behind the necessity of ascertaining correctly the type of response occurring with the IFT, for example asking the patient to make conditional responses.

Merely recording that the hand appeared to move is insufficient. Unfortunately, such unverified responses were used in the principal article quoted by Healy and Pomfrett to suggest that the IFT does not work [8]. Bogod and colleagues [8] used the IFT for the first 30 min of surgery and scored their responses as "nothing, non-specific or firm clenching/flexing". They made no attempt to communicate with the patient. They used a command which asked the patient to open and close her hand if she could hear the message and would rather be more deeply asleep. Bogod and colleagues also classified their patients on the basis of dreams into light and deep groups and assumed that the IFT responses should bear some relationship to this split.

Neither of the two patients reported as being aware [8] showed type-two responses (clenching-flexing responses) but there are major problems in interpreting these data as evidence of intraoperative awareness and failure of the IFT. Patients may not have wished to be more deeply asleep or, as the tape was not personalized with a name, the patients may not have realized the message was intended for them. More importantly, the IFT was used for only 30 min so both experiences (one described discomfort similar to a previous Caesarean section, the other a suffocating feeling) could easily have occurred after this period, particularly during the waking up and extubation period.

It is true that ketamine is believed to disrupt cognitive function, but unlike thiopentone it also provides analgesia. Although the suggestion of Healy and Pomfrett that patients receiving ketamine do not respond to commands because they are conscious with impaired cognition is a possible explanation, it is much more likely that compared with thiopentone, patients who received ketamine were adequately anaesthetized [9].

Sometimes patients respond to a simple command, but do not respond appropriately to more complex commands. While such simple movements in respond to commands might not be a taxing test of cognitive function in the true psychological sense, we do not believe many anaesthetists would be likely to continue surgery without changes to their anaesthetic regimen when they observe a patient squeezing their fingers to a simple command or opening their eyes to command.

In view of the data presented [10, 11], we accept that provided a volatile agent is used appropriately the majority of patients are unconscious during general anaesthesia, but such proof can only be provided by use of the IFT. There is no electronic monitor available which can give real-time quantification of depth of anaesthesia and in its absence we remain firmly of the view that the IFT is the only currently available, real-time, practical method of determining levels of consciousness during general anaesthesia involving neuromuscular block.

I. F. RUSSELL
Department of Anaesthesia
Hull Royal Infirmary
Kingston upon Hull
M. WANG
Clinical Psychology Unit
University of Hull
Kingston upon Hull

1. Russell IF, Wang M. Intraoperative awareness and the isolated forearm technique. *British Journal of Anaesthesia* 1995; 75: 819–820.
2. Healy TEJ, Pomfrett CJD. Intraoperative awareness and the isolated forearm technique. *British Journal of Anaesthesia* 1995; 75: 820–821.
3. Hargrove RL. Awareness under anaesthesia. *Journal of the Medical Defence Union* 1987; 3: 9–11.
4. Bonke B, Jelicic M, Bonebakker AE, De Roode A, Bovill JG. Information processing under anaesthesia. *Anaesthesia* 1993; 48: 820–821.
5. Head-Rapson AG, Devlin JC, Parker CJR, Hunter JM. Pharmacokinetics and pharmacodynamics of the three isomers of mivacurium in health, in end-stage renal failure and in patients with impaired renal function. *British Journal of Anaesthesia* 1995; 75: 31–36.
6. Slavov V, Khalil M, Merle JC, Agostini MM, Rugier R, Duvaldestin P. Comparison of duration of neuromuscular blocking effects of atracurium and vecuronium in young and elderly patients. *British Journal of Anaesthesia* 1995; 74: 709–711.
7. Russell IF. Auditory perception under anaesthesia. *Anaesthesia* 1979; 34: 211.
8. Bogod DG, Orton JK, Yau HM, Oh TE. Detecting awareness during general anaesthetic section. An evaluation of two methods. *Anaesthesia* 1990; 45; 279–284.
9. Baraka A, Louis F, Noueihid R, Diab M, Dabbous A, Sibai A. Awareness following different techniques of general anaesthesia for Caesarean section. *British Journal of Anaesthesia* 1989; 62: 645–648.
10. Wang M, Russell IF. Skin conductance as a measure of anaesthetic depth: typical profile and relation to isolated forearm responses. In: *Proceedings of the Third International Symposium on Memory and Awareness in Anaesthesia*, Rotterdam, June 8–10, 1995 (in press).
11. Russell IF, Wang M. Implicit and explicit memory for intraoperative word stimuli presented in the absence of isolated forearm responses. In: *Proceedings of the Third International Symposium on Memory and Awareness in Anaesthesia*, Rotterdam, June 8–10, 1995 (in press).

Sir,—Thank you again for allowing us to answer yet another of Dr Wang and Dr Russell's letters. Our original letter [1] to *The Times* sought not to chastise these researchers, but rather to temper the conclusions drawn from the original article by a correspondent for *The Times* during April, 1995 [2], which contained the sensational statement that "half of the patients on every operating list show evidence of wakefulness". It is unfortunate that, despite their reported attempts to allay public anxiety in the media, Drs Wang and Russell did not also choose to write to *The Times*. We would then have seen their clarification of the facts, and would not have written any further letters on this subject.

Our statement [3] that opioid anaesthesia "represents a very specific anaesthetic scenario" was not meant to infer that it is a little-used, obscure technique. It was mentioned only because the original article [2] in *The Times* did not mention the anaesthetic technique used, and its title inferred that half of all patients are awake during all anaesthetic procedures. We are glad to note that Drs Wang and Russell agree with us that this is not the case with appropriate levels of other anaesthetics. It is sad that they chose not to reassure readers of *The Times* about the outstanding efficacy of anaesthesia.

It is interesting to note that the failures of the IFT reported in the literature, on which we based our statement "the IFT has been proved to be ineffective," were all, according to Drs Wang and Russell, caused by methodological flaws. Our previous letter [3] discussed the findings of the groups who described the IFT to be ineffective in some detail, and we shall not repeat that discussion here.

If we attempt to attribute something useful to this series of letters, at least they may serve to place the IFT into its proper context. The IFT is, at present, an adjunct to other anaesthetic research. One example of such research [4] used a carefully constructed procedure to define recovery of consciousness in 20 patients after a single dose of thiopentone. The patients were monitored using the IFT and a commercially available EEG monitor (Aspect A-1000). An initial orientating command ("squeeze my fingers") was repeated every 30 s and followed, after a positive response, with a more complex test of cognition ("squeeze my fingers twice"). Only a response to the second condition was taken as proof of recovery of consciousness. This research suggested that the EEG monitor indicated consciousness at least as effectively as the IFT, but with the addition of a continuous, automatic and objective scale (bispectral index). However, neither the IFT nor the bispectral index answer what the anaesthetist really needs to know, that is what is the absolute depth of anaesthesia and is this sufficient to prevent various stimuli during surgery from causing the patient to awaken? As such a monitor, the IFT is ineffective. After all, it is too late if the patient is already awake. That is failure.

T. E. J. HEALY
C. J. D. POMFRETT
University Department of Anaesthesia
University of Manchester
Manchester

1. Healy TEJ, Pomfrett CJD. Patients who remain awake during surgical operations. *The Times* April 18, 1995.
2. Laurance J. Half of patients "awake during surgery." *The Times* April 5, 1995.
3. Healy TEJ, Pomfrett CJD. Intra-operative awareness and the

isolated forearm technique. *British Journal of Anaesthesia* 1995; 75: 820–821.

4. Flashon R, Sebel PS, Singl J. Detection of consciousness following thiopental: Isolated forearm and bispectral EEG (BIS). In: *Proceedings of the Third International Symposium on Memory and Awareness in Anaesthesia*, Rotterdam, June 8–10, 1995 (in press).

CSF progesterone concentrations in pregnancy

Sir,—I read with interest the article by Hirabayashi and colleagues [1] in which the authors showed that there was an increase in CSF progesterone concentrations in pregnancy and a greater cephalad spread of anaesthesia as pregnancy progressed. They were unable to demonstrate any correlation between CSF progesterone concentration and maximum cephalad spread of anaesthesia in any of the groups. However, they claimed that the data suggested that "not only a minimum level of progesterone in CSF but also a certain duration of exposure to elevated CSF progesterone concentrations may be necessary for enhancement of spread of spinal anaesthesia...". Even though they were unable to show a relationship, they seem to want the reader to conclude that progesterone may be related in some way to the higher spread of spinal anaesthesia. They are suggesting causality without any evidence to support it.

All patients had subarachnoid injection of hyperbaric solution which would tend to spread cephalad because of the natural curvature of the spine. One way to avoid the effect of "mechanical factors" on cephalad spread would have been to use an isobaric solution for injection. Spread of isobaric solution is not affected by the position of the patient and other mechanical factors to the same extent as a hyperbaric solution.

The authors have cited several references which support the increased susceptibility of nerve tissue to block by local anaesthetic agents in pregnancy. Mechanisms which have been implicated are the direct effect of progesterone on membrane excitability, indirect actions of neurotransmitters, increased permeability of the neural sheath and potentiation of the analgesic effect of endogenous opioids. These studies can be used to explain an increase in the intensity of subarachnoid block with lignocaine but the references cited cannot explain an increase in cephalad spread of the block.

N. BALIGA
Department of Anesthesiology
University of Michigan Medical Center
Ann Arbor, MI, USA

1. Hirabayashi Y, Shimizu R, Saitoh K, Fukuda H. Cerebrospinal fluid progesterone in pregnant women. *British Journal of Anaesthesia* 1995; 75: 683–687.

Sir,—In our article we demonstrated a time lag between an increase in CSF progesterone concentration and development of enhanced spread of spinal anaesthesia. In addition, enhanced cephalad spread of spinal anaesthesia was found to take place during the middle stage of pregnancy, in spite of its low CSF progesterone concentration. Hence, we concluded that not only a minimum level of progesterone in CSF but also a certain duration of exposure to elevated CSF progesterone concentrations may be necessary for enhanced spread of spinal anaesthesia. Because mechanical factors are insufficient to explain enhanced spread of spinal anaesthesia beginning at the middle stage of pregnancy, an increase in progesterone, as a non-mechanical factor, is expected to play an important role in the enhancement. In addition, our results showed that there was no significant correlation between CSF progesterone concentration and cephalad spread of spinal anaesthesia at any stage of pregnancy, and that cephalad spread did not differ between singleton and twin pregnancies in spite of significantly higher concentrations in CSF progesterone in parturients with twin pregnancies compared with those with singletons. From these data we concluded that the value of CSF progesterone concentration does not correlate directly with the degree of enhancement. This conclusion, however, does not deny involvement of progesterone with pregnancy-induced enhancement of spinal anaesthesia. We presume that a certain duration of exposure to elevated CSF progesterone concentrations causes enhancement of spinal anaesthesia beginning at the middle stage of pregnancy, regardless of the values of CSF progesterone concentration.

We agree with Dr Baliga's suggestion that to avoid the effect of "mechanical factors" on cephalad spread, isobaric anaesthetic solutions are preferable to hyperbaric. Unfortunately, we do not have our own data on cephalad spread with isobaric solution, particularly with respect to pregnant women [1]. On the other hand, Russell and Holmqvist [2] compared the effects of isobaric with those of hyperbaric bupivacaine in parturients undergoing Caesarean section, and suggested that pregnancy enhances the spread of isobaric more than the spread of hyperbaric bupivacaine. Nonetheless, it remains unclear if pregnancy during the early and middle stages enhances the spread of isobaric anaesthetics.

A hyperbaric solution injected into the mid-lumbar subarachnoid space spreads in both cephalad and caudal directions under the influence of gravity. In a cephalad direction, it pools in the lowest part of the thoracic hollow and then diffuses towards cephalad. The concentration of the anaesthetic agent in CSF at the cephalad part of the hollow should be lower than that at the bottom of the hollow. In this condition, a certain concentration that is devoid of local anaesthetic activity in non-pregnant women may cause conduction block in pregnant women who have an increased susceptibility of nerve tissue, resulting in an increase in cephalad spread of block. Thus increased susceptibility of nerve tissue during pregnancy may explain not only the increase in intensity of subarachnoid block but also the increase in cephalad spread of the block. The references cited in our article support the increased susceptibility of nerve tissue to block by local anaesthetics during pregnancy. The cellular mechanism of this effect, however, is not yet clear.

Y. HIRABAYASHI
R. SHIMIZU
K. SAITOH
H. FUKUDA
Department of Anaesthesiology
Jichi Medical School
Tochigi, Japan

1. Hirabayashi Y, Shimizu R, Saitoh K, Fukuda H. Subarachnoid spread of isobaric tetracaine in adolescents. *British Journal of Anaesthesia* 1995; 75: 245–246.
2. Russell IF, Holmqvist LEO. Subarachnoid analgesia for Caesarean section. A double-blind comparison of plain and hyperbaric 0.5% bupivacaine. *British Journal of Anaesthesia* 1989; 59: 347–353.

Extradural analgesia in the first stage of labour

Sir,—We read with interest the article by Buggy and MacDowell [1] comparing an extradural mixture of clonidine and fentanyl with 0.25% bupivacaine for the first stage of labour and wish to raise the following points.

(1) While claiming that the power of the study was too low to detect a true difference in sedation scores (30% power) and the incidence of hypotension (45% power) between the groups, the authors conveniently omitted details of the study's power to detect a difference in analgesic efficacy between the two groups, one of the stated aims of their study. The degree of analgesia, as assessed by visual analogue scores, was said to be similar in both groups, but considering there were only 14 patients in each group, we suspect that the study lacked sufficient power to reveal any difference.

(2) Although the design of the study was said to be double-blind, we believe that the anaesthetist performing the assessments in both groups could not have been truly blinded as to which drug regimen was being used. As the data revealed that eight patients in the 0.25% bupivacaine group, not unexpectedly, developed significant leg weakness, presumably the anaesthetist could not have asked patients in this group to perform a Romberg's test!

(3) The authors found a median sensory level of T10 in both groups, but stated that all patients in the clonidine–fentanyl group had "preserved pinprick and temperature sensation". Are both findings compatible? Perhaps other, unspecified, sensory tests were performed.

(4) The authors stated that overall satisfaction with extradural analgesia after delivery was high in both groups: 79% and 86% in the clonidine–fentanyl and bupivacaine groups, respectively. The implication is that the clonidine–fentanyl mixture provided

good analgesia overall. However, the single dose of clonidine–fentanyl used in group 1 provided analgesia only for a mean of 80 min during a much longer labour (median duration 6.4 h). Both groups subsequently received extradural infusions of 0.1 % bupivacaine in addition to further top-ups of 0.25 % bupivacaine if analgesia was inadequate. There is also no mention of the additional amounts of 0.25 % bupivacaine used in both groups. The implied overall satisfaction with the clonidine–fentanyl mixture must therefore be regarded with scepticism.

(5) The authors stated in conclusion that it may be safer for patients receiving clonidine–fentanyl mixtures to walk during labour compared with a group receiving an ambulatory regimen of 0.1 % bupivacaine with fentanyl 2 $\mu g\ ml^{-1}$ because of reduced dorsal column impairment. However, it is unclear how many individual patients had abnormal dorsal column signs in the clonidine–fentanyl group. For example, did the four patients with impaired proprioception also have impaired vibration sense ($n = 2$) and a positive Romberg's sign ($n = 2$)? Otherwise eight different patients (55 %) could have exhibited abnormal dorsal column signs, precluding ambulation.

(6) Finally, neonatal assessment in the study was inadequate. Umbilical cord blood-gas values and possibly neurobehavioural scoring would have provided additional information on neonatal condition.

R. Fernando
M. G. Parry
Department of Anaesthesia
Royal Free Hospital
London

1. Buggy DJ, MacDowell C. Extradural analgesia with clonidine and fentanyl compared with 0.25 % bupivacaine in the first stage of labour. *British Journal of Anaesthesia* 1996; **76**: 319–321.

Sir,—We thank Drs Fernando and Parry for their interest in our article and respond to their comments sequentially.

(1) Assuming that a reduction of 4 cm on the visual analogue scale (VAS) is a clinically significant reduction in pain intensity, and given a median interquartile range of 2.5 cm on the VAS from all our pain data, the power of our study to detect true differences in VAS scores was 82 %, for an alpha error of 0.05 and $n = 14$ in each group. The reason for our study's apparent greater power to detect differences in pain scores compared with its relatively low power to detect differences in the incidences of side effects lies in the nature of the data: much greater power is required to detect differences in *proportions* between groups than for differences in data on an ordinal scale, especially when, as pointed out in our study, the incidence of these side effects was low

(2) Our hospital pharmacist ensured that our study was double-blind, using coded, labelled syringes. The table in our article indicated MRC < 3, which may have been misleading. Motor weakness was taken as an MRC grade *less than or equal to* 3, and seven of the eight patients in this category were in fact MRC grade 3. All eight patients were able to stand and undertake Romberg's test, although it was deemed abnormal in six.

(3) Sensory level was obtained using a cold ethyl chloride spray, whereas dermatomal sensation was tested with the base of the tuning fork, in addition to pinprick.

(4) All patients received an infusion of 0.1 % bupivacaine after a mean duration of 80 min on the test solutions alone, and although there were no statistically significant differences between the median amounts of bupivacaine infused, there is no doubt that overall patient satisfaction would have been influenced by the analgesia provided by this infusion.

(5) The presence of posterior column signs does not preclude ambulation, as the experience of the Queen Charlotte's group has demonstrated. We suggest a potential for greater safety in the reduction of these transient abnormalities, if the regimen can be shown in future studies to be effective and safe over a longer duration of labour. One patient in our clonidine–fentanyl group had impaired vibration sense alone, otherwise our patients with impaired proprioception also had other posterior column signs.

(6) We accept that umbilical cord gases and neurobehavioural scores would indeed have provided additional information on neonatal condition.

D. Buggy
C. MacDowell
Beaumont Hospital
Dublin, Ireland

Extradurals and infection

Sir,—We read with interest the article by Jakobsen, Christensen and Carlsson [1] on extradural anaesthesia in the presence of infection. Following a case at St Helier Hospital, where there was microbiological evidence of infection in a patient receiving a continuous extradural infusion for postoperative pain relief, we undertook a survey to culture the tips from all non-obstetric catheters used for postoperative pain relief. During the first 6 months, all catheters were inserted with an aseptic non-standardized technique, and during the second 6 months the catheters were inserted with a standardized technique.

The total number of catheters inserted was 136. The overall incidence of contaminated catheters was 19.8 %. There was no significant difference in the incidence of contamination between the two techniques. There was no significant difference in the duration of the period *in situ* between those with a positive culture (mean 72 h) and those with a negative culture (mean 81.7 h). Specific organisms cultured included *Staphylococcus epidermidis* (most common), *Coliform*, *Bacillus*, *Enterococcus* and *Diphtheroid*. Except for the septicaemia seen in the patient described, we saw no other infective complications. Infected extradural catheters carry a serious risk of morbidity and mortality in terms of septicaemia, meningitis and abscess formation. In a review of the literature, we found 34 reported cases of extradural abscess [2–7] and six cases of meningitis [6, 8–14]. There were no reported cases of septicaemia.

Intuitively we would expect the longer an extradural catheter is *in situ* the more likely the patient is to suffer infective complications, in a manner similar to indwelling i.v. catheters. However, this does not seem to be the case from our results or from a study by DuPenn and colleagues [15]. We were, however, surprised by the duration the authors left their catheters *in situ*, as Bromage [16] recommends that catheters should be changed every 72 h to prevent the occurrence of local tissue reactions.

In view of our results, we feel that the use of indwelling extradural catheters in the management of patients who require repeated surgical procedures in the presence of infection cannot be justified as the benefits have not been shown to exceed the risks.

C. M. Brosnan
St George's Hospital
London
M. L. B. Wood
Queen Alexandra Hospital
Portsmouth
M. Wheildon
St Helier Hospital
Carshalton, Surrey

1. Jakobsen KB, Christensen M-K, Carlsson PS. Extradural anaesthesia for repeated surgical treatment in the presence of infection. *British Journal of Anaesthesia* 1995; **75**: 536–540.
2. Nigan Kee WD, Jones MR, Thomas P, Worth RJ. Extradural abscess complicating extradural anaesthesia for Caesarean section. *British Journal of Anaesthesia* 1992; **69**: 647–652.
3. Bollenson E, Prange HW. An epidural spinal abscess as a lethal complication of peridural anaesthetic. *Regional Anaesthesia* 1991; **14**: 101–103.
4. Ericsson M, Algers G, Schliamjer SE. Spinal epidural abscesses in adults: review and report of iatrogenic cases. *Scandinavian Journal of Infectious Diseases* 1990; **22**: 249–257.
5. Kobayashi Y, Shiotani M, Osetok, Naganuma Y, Karasawa H. Six cases of epidural abscess probably caused by epidural block and examination by gadolinium MRI imaging. *Japanese Journal of Anaesthesiology* 1993; **42**: 888–892.
6. Linneman MV, Bulow HH. Infections after insertion of epidural catheters. *Vgeskrift for Laeger* 1993; **155**: 2350–2352.
7. Manourian AC, Dickman AC, Drager BP, Sonntag VK. Spinal epidural abscess: 3 cases following spinal epidural injection demonstrated with M.R.I. *Anesthesiology* 1993; **78**: 204–207.
8. Shintani S, Tanaka H, Iriruni A, Mitoh Y, Udono H, Kaneda A, Shiigai T. Iatrogenic acute spinal abscess with septic meningitis, M.R. findings. *Clinical Neurology and Neurosurgery* 1992; **94**: 253–255.
9. Berga S, Trierweiler MW. Bacterial meningitis following epidural anesthetic for vaginal delivery. A case report. *Obstetrics and Gynecology* 1989; **74**: 437–439.

10. Davis L, Hargreaves C, Robinson PN. Postpartum meningitis. *Anaesthesia* 1993; **48**: 788–789.
11. James FM, Geurse RH, Naiem H, White GJ. Bacteriologic aspects of epidural analgesia. *Anesthesia and Analgesia* 1976; **55**: 187–190.
12. Barrets RS. Bacteriological culture of indwelling epidural catheters. *Anesthesiology* 1962; **23**: 643–646.
13. Hunt JR, Rigor BM, Collins JR. The potential for contamination of continuous epidural catheters. *Anesthesia and Analgesia* 1973; **56**: 222–225.
14. Ready LB, Helper D. Bacterial meningitis in parturients after epidural anesthesia. *Anesthesiology* 1989; **71**: 988–990.
15. DuPenn SL, Petersson DG, Williams A, Bogosian AJ. Infection during chronic epidural catheterisation: diagnosis and treatment. *Anesthesiology* 1990; **73**: 905–907.
16. Bromage PR. *Epidural Analgesia*. Philadelphia: WB Saunders Co, 1978.

Cervical haematoma and airway obstruction

Sir,—We are grateful to Munro, Makin and Reid [1] for their report on cases of airway obstruction after carotid surgery. We have encountered similar problems after anterior cervical spine surgery. We agree with the authors that early intervention is to be encouraged and that deterioration of airway patency is unpredictable and can be rapid; fatalities have occurred in our hospital. The problem is that staff are reluctant to establish a tracheal airway until it is clearly necessary, because they know that the intervention may be difficult and they risk criticism of their management. Professor Eichorn has called anaesthesia a specialty with "zero tolerance for complications" [2].

Munro, Makin and Reid apologize for the use of i.v. induction and neuromuscular block in one of their cases, even though the patient's trachea was intubated successfully. We have not found evidence in theirs or other reports [3] that i.v. induction and paralysis are less likely to be successful than inhalation induction. Airway patency nearly always deteriorates when anaesthesia is induced, for two reasons: (1) the glottic opening obstructs against the posterior pharyngeal wall as pharyngeal tone decreases [4, 5]; and (2) reflex glottic activity (coughing, breath-holding and laryngospasm). Obstruction may occur at light levels of anaesthesia in patients with upper airway pathology whatever method is used, including topical anaesthesia of the glottis [Calder, unpublished observations]. Deep general anaesthesia is required to obtund glottic reflex activity sufficiently to allow intubation. This can be difficult to obtain with an inhalation technique and may be impossible if the airway is obstructed. Our experience with halothane and spontaneous ventilation for fibreoptic tracheal intubation led us to abandon the technique. At least one patient in our series survived only because muscle paralysis and positive pressure ventilation were commenced [6]. In our experience a period of positive pressure ventilation is required to obtain sufficient glottic relaxation when halothane is used. The benefits of positive pressure, or at least CPAP, in the relief of severely obstructed airways have been mentioned by several authors [7–9], and positive pressure is the mainstay of treatment in obstructive sleep apnoea [10]. We do not seek to dissuade our colleagues from using an inhalation technique, but we suggest that it is no more likely to succeed than any other when severe airway obstruction is present. It is unhelpful to give the impression that the use of airway-friendly i.v. agents such as propofol or neuromuscular blockers may expose practitioners confronted with a desperate emergency to criticism.

Our advice to practitioners treating patients with anterior cervical haematomas is: (1) be aware that complete airway obstruction can occur suddenly; (2) inhalation of nebulized adrenaline can improve the airway, but is not a substitute for securing the airway – we have had a fatality in a patient whose airway improved dramatically with adrenaline but obstructed completely some hours later; (3) have a surgeon standing by ready to perform a tracheotomy; (4) awake fibreoptic intubation in the sitting position is a good technique, but be aware that the airway can deteriorate during the procedure because of (1) above, and because lignocaine can provoke laryngospasm when applied to the glottis [11]; (5) insufflate oxygen via a nasal catheter; (6) have a laryngeal mask airway (LMA), a gum elastic bougie and also a 6.0-mm diameter tube to allow through LMA intubation [12]; (7) use whatever method of induction with which you are comfortable and give neuromuscular blockers if the patient may benefit; and (8) use a small tube (7.0-mm diameter maximum) and do not remove it for at least 24 h.

Our aim should be to encourage early intervention by emphasizing that in the early stages any method is likely to be successful, and refraining from criticism if difficulty is encountered, because it is probable that pathology, not technique, is to blame.

I. Calder
K. F. Koh
Department of Neuroanaesthesia
National Hospital for Neurology and Neurosurgery
London

1. Munro FJ, Makin AP, Reid J. Airway problems after carotid endarterectomy. *British Journal of Anaesthesia* 1996; **76**: 156–159.
2. Eichorn JE. Pulse oximetry as a standard of practice in anesthesia. *Anesthesiology* 1993; **66**: 157–162.
3. O'Sullivan JC, Wells DG, Wells GR. Difficult airway management with neck swelling after carotid endarterectomy. *Anaesthesia and Intensive Care* 1986; **14**: 460–464.
4. Boiden MP. Airway patency in the unconscious patient. *British Journal of Anaesthesia* 1985; **57**: 306–310.
5. Nandi PR, Charlesworth CH, Taylor SJ, Nunn JF, Doré CJ. The effect of general anaesthesia on the pharynx. *British Journal of Anaesthesia* 1991; **66**: 157–162.
6. Smith M, Calder I, Crockard HA, Isert P, Nicol ME. Oxygen saturation and cardiovascular changes during fibreoptic intubation under general anaesthesia. *Anaesthesia* 1992; **47**: 158–161.
7. Sparks CJ. Ludwig's angina causing respiratory arrest in the Solomon Islands. *Anaesthesia and Intensive Care* 1993; **21**: 460–462.
8. Riazi J. The difficult pediatric airway. In: Benumof JL, ed. *Airway Management—Principle and Practice*. New York: Mosby, 1995; 585–637.
9. King CJ, Davey AJ, Chandradeva K. Emergency use of the laryngeal mask airway in severe upper airway obstruction caused by supraglottic oedema. *British Journal of Anaesthesia* 1995; **75**: 785–786.
10. Hanning CD. Obsructive sleep apnoea. *British Journal of Anaesthesia* 1989; **63**: 477–488.
11. Sidhu VS, Whitehead EM, Ainsworth QP, Smith M, Calder I. A technique of awake fibreoptic intubation. Experience in patients with cervical spine disease. *Anaesthesia* 1993; **48**: 910–914.
12. Silk JM, Hill HM, Calder I. Difficult intubation and the laryngeal mask. *European Journal of Anaesthesiology* 1991; (Suppl. 4): 47–51.

Sir,—We thank Dr Calder and Dr Koh for their interest in our report.

We appreciate that the safest and most appropriate management of a difficult airway is usually that method with which the anaesthetist feels most confident. However, regarding i.v. induction and paralysis we feel that this may not be as successful, as one or our original references indicates [1]. In a series of six cases, in the four who were paralysed, the lungs could not be ventilated by hand. Two of these patients became asystolic and two suffered bradycardia of which one was less than 10 beat min^{-1}. Of these one had an emergency tracheotomy and in the other three, the trachea was intubated blindly. The two other cases underwent inhalation induction, one after ensuring the ability to hand ventilate was paralysed, and in both the trachea was intubated with comparative ease.

We agree that early intervention is to be encouraged, however, in such cases the degree of airway distortion should never be underestimated, and that a surgical airway may be a safe alternative.

F. J. Munro
A. P. Makin
J. Reid
Western Infirmary
Glasgow

1. O'Sullivan JC, Wells DG, Wells GR. Difficult airway management with neck swelling after carotid endarterectomy. *Anaesthesia and Intensive Care* 1986; 14: 460–464.

Management of pre-eclampsia

Sir,—We read with interest the recent review article by Mushambi, Halligan and Williamson [1] on recent developments in the pathophysiology of eclampsia, and wish to draw attention to a recent case who responded dramatically to Centoxin. It raises several interesting questions and possibilities for future research and management of these patients, particularly in respect of liver damage and possible gastrointestinal failure, some aspects of which were not included in this review article.

The case was a 31-yr-old primigravida who was delivered of a live infant under extradural anaesthesia by Ventouse extraction. She had had an uneventful antenatal course with no sign of pregnancy-induced hypertension, although 2+′ protein were recorded in the urine throughout labour. Three hours after delivery she started to complain of headaches and epigastric pains, at this time she was found to be mildly hypertensive (165/95 mm Hg). Simple analgesia and baseline investigations were ordered. Six hours after delivery she convulsed. Further episodes occurred 1 and 2 h later. While observed on the delivery ward she was given phenytoin and diazepam, but additional treatment with Heminevrin and thiopentone (at low doses) were required to control the convulsions. Unfortunately, there were no intensive care beds available at the time and so management was continued in the delivery suite. Central venous pressure was monitored and urine output (with heavy proteinuria) maintained with careful boluses of human albumin solution. The patient continued to deteriorate, becoming febrile with tachycardia, and a labile arterial pressure, and she showed signs of pulmonary oedema. Serum blood glucose concentration became unstable (reaching as low as 1.2 mmol litre^{-1} at one time) and required supplementary glucose. Biochemical and haematological evidence of worsening multi-organ failure became evident, as her LFT became elevated and haemoglobin decreased to 8.8 g litre^{-1} with a platelet count of 58×10^9 litre^{-1}. It was thought that an ensuing systemic inflammatory reaction syndrome (SIRS) was developing. It was thought unlikely that any products of conception were retained, her urine was clear of organisms and therefore perhaps significant translocation of gut bacteria and endotoxins was occurring. With deranged liver function, especially the reticulo-endothelial aspect, it was possible that this was causing significant endotoxaemia. After much discussion with the intensivists it was decided to administer Centoxin (HA-1A) to this patient (she was already receiving cefuroxime and metronidazole).

Within 4 h she became demonstrably more stable and less agitated. Sedation was stopped and arterial pressure became normal; blood glucose concentration became less erratic. Over the next 8 h the clinical signs of pulmonary oedema stabilized (she had demonstrable cardiomegaly on the chest x-ray) and her temperature returned to normal. All cultures failed to grow organisms. Despite persisting albuminuria, peripheral oedema stabilized over the next 24 h and blood glucose concentrations became normal.

Although it could be argued that this eclamptic patient would have stabilized as rapidly without Centoxin, as she had delivered the fetal–placental unit, it does suggest that significant endotoxaemia was occurring (although we have no proof). Perhaps the phrase "toxaemia of pregnancy" should be retained? It may well be that a form of systemic inflammatory reaction is occurring in this disease as a result of the immunological insult outlined in the review article. There is limited evidence in animal models that gut translocation can contribute to the pathophysiology of eclampsia [2, 3], although little human evidence has yet been published [4].

Clearly, liver impairment contributes to endotoxaemia (and other forms of sepsis from gut organisms), and often this liver damage is neglected in pre-eclamptic and eclamptic patients until severe failure has occurred. Perhaps the "fatty liver of pregnancy" is one form of end-organ failure caused by the same pre-eclamptic process, another being the more easily recognized HELLP syndrome? In this unit we observe carefully for liver impairment and monitor blood glucose concentrations regularly. Other forms of liver support can then be given as needed for acute liver failure [5]. This aspect of end-organ damage was overlooked in the review article and we commend regular blood glucose estimation as the minimum for monitoring liver dysfunction; regular clotting screen and protein–albumin concentrations should also be undertaken. Perhaps the gastrointestinal tract itself should be encompassed in the list of end-organs to fail?

Another form of end-organ damage which may also be part of the pre-eclamptic disease process is that of the heart failure seen in severe eclamptics; perhaps this is part of "cardiomyopathy of pregnancy" and instituted by a similar immunological stimulus.

Clearly more studies are required into the specific immunological problems and complex processes that occur in pre-eclampsia, but perhaps the role of endotoxins could be defined further.

J. E. H. Ward
J. A. Caunt
J. Alderson
Northern General Hospital
Sheffield

1. Mushambi MC, Halligan AW, Williamson K. Recent developments in the pathophysiology and management of pre-eclampsia. *British Journal of Anaesthesia* 1996; 76: 133–148.
2. Faas MM, Schuiling GA, Baller JF, Visscher CA, Bakker WW. A new animal model for human preeclampsia: ultra-low-dose endotoxin infusion in pregnant rats. *American Journal of Obstetrics and Gynecology* 1994; 171: 158–164.
3. Collins JG, Smith MA, Arnold RR, Offenbecher S. Effects of *Escherichia coli* and *Porphyromonas gingivalis* lipopolysaccharide on pregnancy outcome in the golden hamster. *Infection and Immunology* 1994; 62: 4652–4655.
4. Laham N, Brennecke SP, Bendtzen K, Rice GE. Tumour necrosis factor alpha during human pregnancy and labour; maternal plasma and amniotic fluid concentrations and release from intrauterine tissues. *European Journal of Endocrinology* 1994; 131: 607–614.
5. Stanley AJ, Lee A, Haynes PC. Management of acute liver failure; aetiology, complications and management. *British Journal of Intensive Care* 1995; 5: 8–15.

Sir,—We thank Drs Ward, Caunt and Alderson for their interest in our review article and are grateful for their comments. We are unable to comment on their theory of endotoxaemia or the role of Centoxin, but we wish to make some points.

First, Centoxin was withdrawn from use in 1993. This raises the question of why it was used, unless of course the case described occurred before 1993.

We also wish to question their management of eclampsia using phenytoin, diazepam, chlormethiazole (Heminevrin) and "low-dose" thiopentone. The use of magnesium sulphate in this patient would have been a preferable choice of drug. Compared with diazepam and phenytoin, magnesium sulphate has been shown to control convulsions, reduce recurrent convulsions and cause fewer side effects [1]. The use of chlormethiazole in the treatment of eclampsia is unacceptable because of the problem of fluid overload and oversedation. Magnesium sulphate is now the drug of choice in patients with eclampsia.

From the clinical signs described and laboratory findings stated, it is most likely that the above patient had HELLP syndrome, and hypoglycaemia is a known complication of this syndrome, as stated in our article [2, 3].

Pulmonary oedema in patients with pre-eclampsia results commonly from fluid overload and less frequently from left ventricular dysfunction. Unfortunately the letter does not indicate the type or amount of fluid their patient received, her urine output or central venous or pulmonary wedge pressures; these data would have been helpful in determining the cause of her pulmonary oedema.

Unfortunately, pre-eclampsia is still a disease for which many theoretical and improved aetiologies abound and because it is a multisystem disorder, it has many ways of presenting.

M. C. Mushambi
A. W. Halligan
K. Williamson
Leicester Royal Infirmary
Leicester

1. The Eclampsia Trial Collaborative Group. Which anti-

convulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet* 1995; **345**: 1455–1463.

2. Egley CC, Guthlip JA, Bowes WA. Severe hypoglycemia associated with HELLP syndrome. *American Journal of Obstetrics and Gynecology* 1985; **152**: 576–577.
3. Mushambi MC, Halligan AW, Williamson K. Recent developments in the pathophysiology and management of pre-eclampsia. *British Journal of Anaesthesia* 1996; **76**: 133–148.

ERRATUM

British Journal of Anaesthesia 1996; **76**: 284–291

p. 287. In the legend for figure 2, "......elevated initial Fa_{O_2} (0.08)" should read "......elevated initial $\boldsymbol{Fa}_{CO_2}$ (0.08)"

We apologize to the authors for this confusion which arose during the editorial process.

British Journal of Anaesthesia 1996; **76**: 891–893

BOOK REVIEWS

Anesthesiology, House Officer Series. A. J. Berry and G. B. Knos (editors). Published by Waverly Europe Ltd, London. Pp. 677; indexed; illustrated. Price £9.95.

The publishers describe this series of books as being appropriate to keep in the pocket, but the binding of the book is not strong enough and its size will prohibit it from being easily carried in the pocket.

This book consists of 23 chapters and six appendices, it has 33 contributors, and consequently the chapters lack a consistent approach. Most unfortunately, the first page of chapter 1 has a major printing error, whereby the majority of the first paragraph is repeated; this inevitably colours one's judgement when setting out to review the text.

The chapters cover the whole of anaesthesia, there is frequent use of tables which provides clarity and the appendices on monitoring standards, ACLS and drugs used in anaesthesia are extremely useful. The index is comprehensive and its compilers should be commended.

There are well known differences in practice between North America and the UK and this book is testimony to that fact, for example there are only seven lines of text allocated to the laryngeal mask airway, blood-gas values are quoted in "torr" and the use of an amnesic agent is recommended for insertion of unpleasant monitoring cannulae. As a result of these and many other differences, I do not believe that this book can be recommended for use by the new anaesthetic junior in the UK, as the differences will only serve to confuse and complicate their early formative time in theatre.

G. W. Jones

Ophthalmic Anaesthesia—A Practical Handbook, 2nd Edn. G. Barry Smith, R. C. Hamilton and C. A. Carr. Published by Arnold, London. Pp. 284; indexed; illustrated.

The role of the anaesthetist in the management of patients undergoing ophthalmic surgery has changed markedly in the past decade. There is now much greater emphasis on involvement in procedures during local anaesthesia and there have also been significant changes in surgical practice, an understanding of which is essential for any anaesthetist who wishes to take a full part in patient management. The authors rightly believe that a firm grounding in relevant basic science is an essential prerequisite and the chapter on the anatomy of the eye and orbit is an excellent résumé of current knowledge. Although the illustrations are not in colour they are of very high quality and are adequate for their purpose. Chapters on the physiology of the eye and the effect of drugs on the eye are short but relevant. The section on medical conditions is less appropriate and I doubt the need to consider management of cardiac ischaemia or hypertension even briefly. The discussion of regional compared with general techniques is an area of particular concern to the clinician and is well covered and referenced. There is a full description of techniques of orbital regional anaesthesia and their complications, and many individuals will be interested to note the authors' recommendation that those who wish to practise these should undertake cadaver dissection of the orbital region as part of a training programme. Chapters on general anaesthesia and monitoring, paediatric anaesthesia, strabismus, adnexal surgery, ocular trauma, day-case surgery, vitreo–retinal surgery and audit follow.

The overall impression of this text is that it is written by individuals with considerable personal experience in the field. It is very readable and some of the comments, such as the one on cadaver dissection, are thought provoking. Others are perhaps inappropriate for those in the UK, for example although many ophthalmologists sub-specialize, I doubt that many ophthalmic anaesthetists specialize in anaesthesia for particular surgical procedures. It is an excellent book for those working in the field and many consultants will want a personal copy. Not all trainees are required to know all that is contained in it, but it should find a place in departmental libraries for reference.

W. A. Chambers

Difficult Hypertension: Practical Management and Decision Making. M. J. Kendall, N. M. Kaplan and R. C. Horton (editors). Published by Martin Dunitz, London. Pp. 296; indexed; illustrated. Price £49.95.

Several major text books of hypertension have appeared recently, raising the question "Is there room for one more?" In the case of this book, my answer is yes, because it fills a gap, providing practical approaches to the difficult clinical problems in hypertension. This is a multi-author book, comprising 16 chapters, divided into four sections, dealing with different ages and ethnic backgrounds of patients, types of hypertension, the setting, that is renal disease and diabetes, and decision making in hypertension. Section one concerns hypertension in childhood, pregnancy, the elderly and different ethnic groups. In general the chapters were well balanced but there were several odd recommendations such as the use of i.v. diazoxide for severe hypertension in children. Diazoxide is a powerful and the least controllable form of therapy for acute reduction in arterial pressure with the danger of prolonged severe hypotension. Also, only short-acting ACE inhibitors were recommended, requiring multiple doses throughout the day when surely a single daily dose of a long-acting agent would be preferable. The chapter dealing with hypertension in pregnancy emphasized the clear differences between patients with essential hypertension in pregnancy and those who develop hypertension which is associated with pregnancy; this chapter contained good general advice about management and emphasized important differences in management philosophy. The last chapter in this section on ethnic differences examined the greater severity of hypertension in Blacks and their different responses to antihypertensive therapy, in particular that ACE inhibitors and beta-blockers lower arterial pressure in the White population whereas calcium antagonists and thiazide diuretics are much more effective in the Black population.

The second section entitled "The setting" dealt with secondary hypertension, the problem of "J" shaped curve of cardiovascular risk and reductions in arterial pressure in patients resistant to treatment and the importance and practical difficulties in treating isolated systolic hypertension. These are most important areas in hypertension. I particularly enjoyed the chapter on resistant hypertension which outlined thoroughly sensible and practical approaches for managing these patients. The chapter on the "J" shaped curve marshalled a great deal of evidence to suggest that lowering arterial pressure to less than 85 mm Hg provided no additional benefit and may even be associated with an increase in cardiovascular mortality. Although controversial, this topic is perhaps not one of the most challenging aspects of treatment because large numbers of patients remain untreated or poorly controlled. In my opinion, the problem of reducing a patient's arterial pressure to less than 85 mm Hg diastolic is not a major concern.

The third section covered particular patient settings, including diabetes, cerebrovascular disease, renal failure and a chapter on practical advice on the management of hypertensive patients undergoing anaesthesia. The chapter on cerebrovascular disease dealt with the difficult problem of reducing arterial pressure in stroke patients. Advice about cautious reduction in severe hypertension in acute stroke patients was balanced with the strong message that in the long term, good arterial pressure control is a significant factor in preventing recurrence and improving the long-term outcome of these patients. Only one chapter (12) was aimed at the anaesthetist and gave excellent advice on how to deal with hypertensive patients who require general or spinal anaesthesia. The importance of information on the presence of end-organ damage, in particular the presence of left ventricular hypertrophy which may predispose patients to arrhythmias during induction, was emphasized. The dangers of excessive reductions in arterial pressure during general anaesthesia were discussed, attention being drawn to the role of vascular structural changes leading to thickening of the wall and narrowing of the lumen of blood vessels which limits the ability to increase blood flow in crisis situations.

The fourth and final section of the book concerned decisions relating to the processes involved in introducing a new antihypertensive agent into clinical practice, the impact of antihypertensive therapy on the quality of life of treated patients and how to assess clinical trial data. Quality of life has become an important issue as hypertension is an asymptomatic condition requiring long-term treatment, and treatment should not adversely affect the patient's lifestyle. The final chapter of the book is worth reading by anyone in clinical practice. It outlines a logical approach for evaluation of studies and provides useful rules to test the validity of any clinical study. Limitations of meta-analysis are discussed and provide some understanding of why experts may make different recommendations based on the same clinical data. I very much enjoyed this chapter and commend it to all clinical students and doctors.

H. Thurston

Acute Pain Management: A Practical Guide. P. E. MACINTYRE AND L. B. READY. Published by WB Saunders Co. Ltd, London. Pp. 198; indexed; illustrated. Price £14.95.

There has been an enormous expansion in the provision of acute pain services world-wide over the past decade and there is a need for a small book which can be accessed readily by all involved in this activity. Such a book should be useful for anaesthetists, surgeons, nurses, physiotherapists, pharmacists and other paramedical staff. *Acute Pain Management: A Practical Guide*, by Pamela Macintyre and Brian Ready, more than fulfils this niche. It is an excellent publication and I recommend it highly.

The relatively small volume (198 pages) covers the theoretical and practical aspects of acute pain management in a clear and concise manner. There are nine chapters, many figures, tables and specimen charts, and a short but useful index. In my view, the authors have omitted nothing of importance in this book and its style and depth have been pitched perfectly.

The pharmacology of analgesics and local anaesthetics is described with emphasis on those points which are important in the practical management of patients. The pros and cons of traditional opioid administration are described and there is, of course, a chapter describing patient-controlled analgesia. This latter chapter is particularly good and the theoretical knowledge and practical experience of the two authors shine out from the pages. Extradural and intrathecal analgesia are given the same excellent treatment. The final chapter describes the importance and practical aspects of education of medics, nursing staff and patients.

The style of this book is most impressive; there is hardly a wasted or redundant sentence. Consequently, an enormous amount of factual detail and practical advice is included in this small volume.

I cannot recommend this book too highly. It represents essential reading for those involved in acute pain management and is also extremely good value for money.

D. Rowbotham

Anaesthesia for Surgery of the Spine. S. S. PORTER (editor). Published by Blackwell Science, Oxford. Pp. 390; indexed; illustrated. Price £47.50.

Anaesthesia for spinal surgery is one of those areas in anaesthetic practice which, although it demands special expertise, has not yet acquired the cachet of a subspecialty. In the UK, spinal surgery lies uneasily between neurosurgery, orthopaedics and paediatrics, the emphasis often being dictated by local enthusiasm and custom. Spinal operations may, therefore, be performed in several different units in a region even though there would seem to be substantial clinical and training advantages in concentrating most of these in a spinal surgery unit. Anaesthesia for this type of surgery embraces elements of that used in neurosurgery, orthopaedic and paediatric surgery. There is a particular risk of iatrogenic damage to nervous structures (including the spinal cord) both by the surgeon at operation and by the anaesthetist during manipulation of the neck during laryngoscopy and tracheal intubation.

This is a multi-author book with 20 contributors from a variety of medical institutions in the USA. Although the emphasis is on anaesthesia, there is a substantial surgical contribution which occasionally threatens to dominate. The book is broad in scope, with chapters on the anatomy and physiology of the spinal cord, acute and chronic spinal cord injury, and consideration of surgical procedures involving the cervical and thoracic spine. There are chapters on anaesthesia for spinal surgery in different arthritic conditions, including rheumatoid arthritis and ankylosing spondylitis, thoracolumbar spine correction, radiculopathy and discectomy, and paediatric spine procedures. Electrophysiological monitoring, intensive care management of cervical cord injury and chronic pain after spinal cord injury are considered in depth. Very usefully, the text carries a large number of references, each chapter, therefore, serving as a review of its topic.

Perhaps inevitably there is some repetition. For example, the approach to tracheal intubation in a patient with a proven or suspected cervical spine injury is considered by different authors in chapters 3 and 4; recognition and treatment of venous air embolism is covered equally comprehensively in chapters 4 and 5. The tone throughout, however, is discursive rather than didactic and there are no serious contradictions. There is much that is good, including a review of the anatomy of the adult spinal column (but not that of the child or adolescent), drug-based therapies for acute spinal cord injury, electrophysiological monitoring of the spinal cord and some challenging ideas on living with quadriplegia.

Those sections dealing with anaesthetic techniques describe standard methods for the operations concerned. Topics such as patient positioning, monitoring, hypersensitivity reactions (latex allergy) and assessment and management of the unstable or immobile neck are covered fully. Laryngeal masks, EMLA cream and parental presence at induction are not mentioned and the following topics are addressed very superficially: postoperative monitoring of patient-controlled analgesia (PCA) and extradural analgesia; management of postoperative nausea and vomiting, even in the context of extradural opioids or PCA. The suggestion (p. 190) that the total dose of i.v. infused opioids after thoracolumbar spine surgery can be reduced by giving intrathecal morphine is deplorable.

Notwithstanding these criticisms, this is a readable book containing a fund of useful information not found readily in other single volumes. There are many diagrams, radiographs and scans, although figure 10.10 has an error—the headings "Before" and "After" placed above the columns should refer to rows. The book cannot be recommended unreservedly but would form useful supplementary reading for trainees or those engaged in anaesthesia for spinal operations who wish to refresh their knowledge. It is hardbound, well presented and carries a detailed index.

J. P. H. Fee

Understanding Anaesthesia, 3rd Edn. L. E. S. CARRIE, P. J. SIMPSON AND M. T. POPAT. Published by Butterworth–Heinemann, Oxford. Pp. 431; indexed; illustrated. Price £25.00.

A book which reaches its third edition is clearly established, even more so when a previous edition has been reprinted on several occasions. *Understanding Anaesthesia* is such a book. Its stated aim is the education of the non-anaesthetist who is required to work closely in the anaesthetic environment, for example, operating department personnel, recovery room nurses, anaesthetic assistants, etc. To be successful at this level the book must strike the correct balance between over-simplification and excess complexity. It must also remember the intended audience at all times. In all of these matters it succeeds, hence its established position.

Understanding Anaesthesia contains 431 pages of text which are divided into 47 chapters. One-third of the chapters are of six pages or less and two-thirds are 10 pages or less; only two are more than 14 pages in length. The text is thus concise and confined to the important points only. The information is not too tightly packed however. Good use is made of headings and subheadings and the style is easy to read. The chapters range from fundamental basics, for example applied anatomy and physiology, and interpretation of the ECG, to the more specialized, for example anaesthesia for open heart surgery and neurosurgery. All of the major topics are covered and it is inappropriate to single out any one chapter or section because all are of an equally high standard.

It is difficult in a book such as this to know where to stop and how much detail to include. It is comforting to see that many of the newer drugs and techniques are included. Sevoflurane and desflurane are described and the cardiopulmonary resuscitation guidelines are the latest versions, although some other new agents, for example rocuronium and tramadol are missing. There are, as expected, no fundamental omissions, although the theory and use of the Swan Ganz catheter receives only brief coverage. Any desire for further information is amply catered for by the inclusion of a suggested list of books for further reading.

This is a book which deserves a place in every hospital library. It should also be on the reading list for all relevant nursing and further educational courses. In addition, copies should be available in strategic areas in operating theatre suites to serve as a general bench-book and as a source of information for students and learners. I am certain that this book will, is common with its previous editions, prove to be a bestseller.

B. J. Pollard

Neuromuscular Block. S. FELDMAN. Published by Butterworth–Heinemann, Oxford, Pp. 180; indexed; illustrated. Price £30.00.

You may ask "Do we need yet another book on neuromuscular block, there have been so many in recent times?" However, this monograph is different. The author has studied neuromuscular function for 40 yr; he has had the good fortune to be guided in his formative period by such great men as Organe, Scurr, Wyman and Lucien Morris. These famous contributors to anaesthetic research were able to teach the next generation to think and inquire; if only we had the same stimuli today! Professor Feldman has written his own soliloquy, raising in print those difficult questions he has always loved, in his most gentlemanly fashion, to ask the aspiring research worker (cognizant that none of us really knows the answer). All who are obsessed by the physiology and pharmacology of neuromuscular transmission will want to read this little book at leisure, and to have ready access to the occasionally idiosyncratic thoughts of (chairman) Feldman on his favourite subjects. It will not be read for its factual content, but to obtain a different perspective; for this book is not mundane, it aims to stimulate and provoke, and to a large extent it achieves these aims. The book presumes some prior knowledge of its subject: it is not intended to detail every latest advance, but to highlight the interesting developments and question the explanations, especially in relation to Professor Feldman's own research work.

The opening chapter on historical perspectives will attract interest, as will those on neuromuscular physiology. Indeed, throughout the text there are informative historical facts which I found noteworthy. None of the chapters is long, some are perhaps too short; they are simply tasters, which contain the pertinent points. The chapter on acetylcholine formation and metabolism is particularly interesting; how long will it be before we know the full answers on the putative presynaptic acetylcholine receptor? Is there more than one subtype for the examination candidate to remember. Do anticholinesterases really have any effect at these presynaptic receptors? The chapters are not referenced in detail, but the relevant literature is given. They are bountifully illustrated, making the book easy to read. My only real disappointment was chapter 8 on pharmacokinetics and pharmacokinetic models; it was so short and opinionated as to be barely worth publishing. I would also have hoped that Professor Feldman might be less nihilistic about obtaining a rapid onset nondepolarizing agent, the ultimate goal of neuromuscular pharmacologists. But in this matter, he has the same view as many of his illustrious contemporaries.

Unlike the great composers, perhaps Professor Feldman's greatest works were his earliest. He will always be remembered for his autoradiographic studies (1969), and his publications on the altered effects of neuromuscular blocking drugs in the presence of acidaemia, alkalaemia (1963) or hypothermia (1973). Similarly, his isolated arm technique (1970) is a novel method of studying drug affinity for the postsynaptic nicotinic receptors and recovery from neuromuscular block. It has been used repeatedly to contrast the action of every new neuromuscular blocking agent, as each has become available. Much attention is paid in the text to these areas of the author's particular interest.

This book is not a reference book; as is so characteristic of the author, it is to be read for enjoyment. It is the heritage which Professor Feldman passes on to his successors; those who inherit it have a formidable challenge in maintaining such standards. I am proud to have known him, and shall ask Professor Feldman to autograph my copy at the earliest possibly opportunity!

J. M. Hunter

A Physicians's Guide to the Internet. L. HANCOCK. Published by Lippincott–Raven, New York. Pp. 232; indexed. Price £23.00.

Having recently acquired access to email and the Internet, I was delighted to be given the task of reviewing *A Physician's Guide to the Internet* by Lee Hancock. I had a superficial knowledge of these things but after reading and using this book I now consider myself as something of any authority!

Lee Hancock is an educational technologist who "by night...explores the Internet looking for anything to do with resources in health and medicine." *A Physician's Guide to the Internet* is the result of this activity.

In the introductory section there is a very useful chapter indeed; a glossary of common Internet terms. I now know my Gopher from my elbow and the difference between Archie and Veronica. I have realized also that many of my "Internet-aware" colleagues are not quite as knowledgeable in this area as they would have me believe. For example, having read this book one can look a colleague straight in the eye and ask with confidence "What exactly do you mean by NCSA Mosaic?" The effect is awesome.

The author describes the Internet very well, for example how to access it and the tools available for finding what you want. Clear descriptions over relatively few pages indicate that it is really very simple and easy to understand.

The second section is the guide to the Internet. It is a list of Internet addresses with short summaries of the information available at each site. There are numerous entries listed under headings such as specific diseases or specialties. Naturally, I homed in on the "anesthesiology" section. Five addresses are listed, all in the USA. With eager anticipation I logged in, or tried to. However, what the first section of the book did not highlight is the eternal wait one often has before getting a response from a web site. This is particularly so when accessing from Europe to the USA. I was therefore unable to access the information "available" at these sites in any great detail. However, I was able to confirm that they really were out there. (The reviewer freely admits that he did not try at 03:00 on a Sunday when apparently the Internet is less busy.)

Access is, of course, quicker if the site is in Europe or elsewhere and therein lies my complaint about this book—the vast majority of listed sites are in the USA. It may be that there are no medical sites in the rest of the world, but I doubt it. The implied criticism of US colloquialism applies also to the appendix, listing Internet Access Providers and Medical School Gophers, all in the USA. In my view, this is a serious deficiency of the book—it seems to me that the whole point of the Internet is that it is world-wide.

I found the first section of this book very good and would recommend it. However, from a world-wide perspective, there is no doubt that the impression given by the author, that there are no medical sites on the Internet outside the USA, is very disappointing. A more appropriate title would be "A Physician's Guide to the Web Sites in the USA".

D. Rowbotham

AUTHOR INDEX

VOLUME 76

British Journal of Anaesthesia

ARS = Anaesthetic Research Society Abstracts

EACTA = European Association of Cardiothoracic Anaesthesiologists

C = Correspondence

E = Editorial

R = Book Review

e = Erratum

Abboud, T. *see* Lee, J. S., (*C*) 169–170
Abdel-Gaffar, M. E. *see* Abdulatif, M. 239–244
Abdulatif, M., Al-Ghamdi, A., Al-Sanabary, M. and Abdel-Gaffar, M. E. Edrophonium antagonism of intense mivacurium-induced neuromuscular block in children 239–244
Åberg, B. *see* van der Linden, J., (*EACTA*) A.84
Adachi, T. *see* Kurata, J. 721–725
Adams, A. P. *see* West, M. R. J. 673–679
Adiseshiah, M. *see* Baranowski, A. P., (*C*) 882–883
Adriaensen, H. A. *see* Vercauteren, M. P. 731–733
Aguilar, J. L., Rincón, R., Domingo, V., Espachs, P., Preciado, M. J. and Vidal, F. Absence of an early pre-emptive effect after thoracic extradural bupivacaine in thoracic surgery 72–76
Akazawa, S. *see* Ikeno, S. 573–575
van Aken, H. *see* Capouet, V. 54–60
Aksoy, N. *see* Özyurt, A., (*EACTA*) A.25
Alahuhta, S. *see* Karinen, J. 616–620
Alderson, J. *see* Ward, J. E. H., (*C*) 889
Aldridge, L. A. *see* Semple, D. 310–312
Al-Ghamdi, A. *see* Abdulatif, M. 239–244
Allen, J. D. and Herity, N. A. Prospects for management of peripheral vascular failure in septic shock, (*E*) 177–178
Allman, C. *see* Grebenik, C., (*EACTA*) A.76
Al-Sanabary, M. *see* Abdulatif, M. 239–244
Al-Shaikh, B. and Stacey, S. *Essentials of Anaesthetic Equipment*, (*R*) 751
Althaus, U. *see* Walpoth, B. H., (*EACTA*) A.7; (*EACTA*) A.58
Amari, B. *see* Paino, R., (*EACTA*) A.40
Andrews, C. J. *see* Daniell, C. J., (*ARS*) 586–587P
Andrews, P. J. D. *see* Souter, M. J. 744–746
Anthuber, M. *see* Welte, M. 90–98
Appadu, B. *see* Stanley, G. 484–486
Appadu, B. L. and Lambert, D. G. Interaction of i.v. anaesthetic agents with 5-HT$_3$ receptors 271–273
Aquilina, R. *see* Crabb, I. 795–801
Arendt-Nielsen, L. *see* Roth, D. 38–42; Wilder-Smith, O. H. G. 816–821
Armstrong, M. *see* Turner, G. 606–610
Arowsmith, J. E., Stygall, J., Timberlake, N., Shah, T., Newman, S. P., Harrison, M. J. G. and Pugsley, W. B. Double blind, placebo controlled study of the effects of remacemide HCl on neuropsychological deficits following coronary artery surgery, (*EACTA*) A.83
Arseniev, L. *see* Leuwer, M., (*ARS*) 585P
Asai, T., Barclay, K., McBeth, C. and Vaughan, R. S. Cricoid pressure applied after placement of the laryngeal mask prevents gastric insufflation but inhibits ventilation 772–776
Asbury, A. J. *see* Fletcher, G. C. 20–22; Levack, I. D. 567–569; Tzabar, Y. 194–197
Astudillo, R. *see* van der Linden, J., (*EACTA*) A.84
Aubas, P. *see* Biboulet, P. 81–84
Auboyer, C. *see* Molliex, S. 151–153
Audibert, G. and Donati, F. Factors governing onset of neuromuscular block, (*C*) 597–598
Aykaç, Z. *see* Süzer, Ö., (*EACTA*) A.9; Süzer, Ö, (*EACTA*) A.68

Baba, H. *see* Denda, S. 258–265
Babic, M. *see* Jovic, M., (*EACTA*) A.49
Bach, A. *see* Schmidt, H. 707–712
Bacher, A. *see* Laßnigg, A., (*EACTA*) A.18
Baddoo, H. H. K. *see* Poulton, B. B., (*EACTA*) A.15
Baele, Ph., D'hoore, W., Bureau, M., Laurent, S. and Stordeur, S. Anaemia and transfusion; major determinants of pressure sores after cardiac surgery, (*EACTA*) A.60
Baele, Ph. *see* Deneys, V., (*EACTA*) A.56; Vuylsteke, A., (*EACTA*) A.50
Bak, P. *see* Roth, D. 38–42
Baker, A. B. *see* Joyce, C. J. 292–296
Baker, R. D. *see* Martlew, R. A. 308–309
Bakhamees, H. S. *see* Naguib, M., (*e*) 339
Balakrishnan, V. R. *see* Thorpe, S. J., (*ARS*) 576P
Baliga, N. CSF progesterone concentrations in pregnancy, (*C*) 886
Banks, R. E. *see* Pittard, A. J. 629–631
Baranowski, A. P. and Adiseshiah, M. Aortic stent surgery, (*C*) 882–883
Barclay, K. *see* Asai, T. 772–776
Barker, I. Cost of volatile agents, (*C*) 749
Barlas, A. *see* Süzer, Ö., (*EACTA*) A.9
Barr, G. *see* Gårdebäck, M., (*EACTA*) A.36
Bastien, O. *see* Paulus, S., (*EACTA*) A.73; Vedrinne, C., (*EACTA*) A.85
Baylot, D. *see* Molliex, S. 151–153
Beaufort, A. M., Nigrovic, V., Proost, J. H. and Wierda, J. M. K.H. Onset time of neuromuscular block is determined by the pharmacokinetics of the blocking drug, (*ARS*) 580P
Bednarkiewicz, M. *see* Licker, M. 632–639
de Beer, N. A. M., van Hooff, J. C., Cluitmans, P. J. M., Korsten, H. H. M. and Grouls, R. J. E. Haemodynamic responses to incision and sternotomy in relation to the auditory evoked potential and spontaneous EEG 685–693
Beisel, B. *see* Brase, R., (*EACTA*) A.47
Bellamy, M. C., Young, Y., Guillou, P. J. and O'Beirne, H. Effects of dopamine and dopexamine on splanchnic microcirculation during major surgery in humans, (*ARS*) 587P
Bellamy, M. C. *see* Enright, S., (*ARS*) 587–588P; O'Beirne, H., (*ARS*) 592P; Pittard, A. J., (*ARS*) 587P; Snook, N. J. 740–743
Benetreau, D. *see* Biboulet, P. 81–84
Bengtsson, L. *see* van der Linden, J., (*EACTA*) A.82
Benhamou, D. *see* Lentschener, C., (*C*) 882
Benson, J. P. and Hutton, P. Use of i.m. temperature probes during cardiopulmonary bypass in humans, (*C*) 472
Benussi, S. *see* Guarracino, F., (*EACTA*) A.45
van den Berg, A. A. Comparison of ondansetron and prochlorperazine for the prevention of nausea and vomiting after adenotonsillectomy 449–451
Berger, R. *see* Hiesmayr, M., (*EACTA*) A.32
Bergh, C.-H. *see* Haraldsson, Å., (*EACTA*) A.27
Berkenbosch, A. *see* Dahan, A. 374–381; (*C*) 747
Berrada, K. R. *see* Tournadre, J. P. 130–132
Berry, A. J. and Knos, G. B., (editors) *Anesthesiology, House Officer Series*, (*R*) 891
Biboulet, P., Capdevila, X., Benetreau, D., Aubas, P., d'Athis, F. and du Cailar, J. Haemodynamic effects of moderate normovolaemic haemodilution in conscious and anaesthetized patients 81–84
Bilgen, F. *see* Toraman, F., (*EACTA*) A.21
Birrell, H. *see* Levack, I. D. 567–569
Bjerring, P. *see* Roth, D. 38–42
Björkman, J.-A. *see* Nordlander, M., (*EACTA*) A.24

Blake, D. *see* Turner, G. 606–610
Blanc, P. *see* Filley, S., (*EACTA*) A.63
Blogg, C. E. *see* Kitching, A. J. 874–876
Boer, F., Olofsen, E., Bovill, J. G., Burm, A. G. L., Hak, A., Geerts, M. and Wetselaar, K. E. Pulmonary uptake of sufentanil during and after constant rate infusion 203–208
Böhmert, F. *see* Brase, R., (*EACTA*) A.47
Böhrer, H. Porphyria, propofol and rats, (*C*) 172
Böhrer, H. *see* Schmidt, H. 707–712
Boisseau, M. R. *see* Freyburger, G. 519–525
Bojic, M. *see* Jovic, M., (*EACTA*) A.49
Boltz, G. *see* Hiesmayr, M., (*EACTA*) A.32
Bompard, D. *see* Lehot, J. J., (*EACTA*) A.43
Bonnefoy, E. *see* Filley, S., (*EACTA*) A.63; Vedrinne, C., (*EACTA*) A.66
Bonnet, F. *see* Gentili, M. 872–873
Booij, L. H. D. J. *see* Vanlinthout, L. E. H. 389–395
Booker, P. D., Taylor, C. and Saba, G. Perioperative changes in α_1-acid glycoprotein concentrations in infants undergoing major surgery 365–368
Booker, P. D. *see* Karmakar, M. K. 811–815
Bosnjak, Z. J. *see* Mazzeo, A. J. 841–846
Bouletreau, P. *see* Tournadre, J. P. 130–132
Bourel, P. *see* Pétrie, J., (*EACTA*) A.54
Bouvier, H. *see* Filley, S., (*EACTA*) A.63
Bovill, J. G. *see* Boer, F. 203–208
Bower, S. *see* Gormley, W. P. 802–805
Bowie, R. A. *see* Levack, I. D. 567–569
Boyd, A. H., Eastwood, N. B., Parker, C. J. R. and Hunter, J. M. Comparison of the pharmacodynamics and pharmacokinetics of an infusion of *cis*-atracurium (51W89) or atracurium in critically ill patients undergoing mechanical ventilation in an intensive therapy unit 382–388
Boyd, O. and Grounds, R. M. Effects of propofol and isoflurane on right ventricular function, (*C*) 598; Gastric tonometry, (*C*) 750
Boys, R. J. *see* Thomas, D. G. 61–65
Bozkurt, K. *see* Süzer, Ö., (*EACTA*) A.9
Braid, D. P. *see* Levack, I. D. 567–569
Braithwaite, P. *see* Mallick, A., (*C*) 335
Brånström, R. *see* Selldén, E. 227–234
Brase, R., Krug, A., Beisel, B., Manhold, C., Stickel, R., Kuckelt, W. and Böhmert, F. Does perioperative transoesophageal echocardiography change the therapy of cardiothoracic patients? (*EACTA*) A.47
Brennum, J. *see* Ilkjaer, S. 829–834
Briquet, F., Harmand, M. F. and Isetta, C. Comparative assessment of the biocompatibility of 4 types of tubing for cardiopulmonary bypass, (*EACTA*) A.31
Broka, S., Ducart, A., Collard, E., Dursin, A., Delire, V., Mayné, A., Randour, P., Marchandise, B. and Joucken, K. Doppler-derived left ventricular DP/DT: peroperative feasibility of the method during mitral valve surgery, (*EACTA*) A.44
Broomhead, C. J. *see* Toner, C. C. 347–351
Brosnan, C. M., Wood, M. L. B. and Wheildon, M. Extradurals and infection, (*C*) 887–888
Brown, B. B. jr *see* Fink, E. J. jr, (*R*) 173
Brown, J. H. *see* Fletcher, G. C. 20–22
Brownridge, P. *see* Elliott, D. W. 322–324
Brunat, G. *see* Ryckwaert, F., (*EACTA*) A.34
Brundin, T. *see* Selldén, E. 227–234
Brunner, M. D., Nathwani, D., Rich, P. A., Thornton, C., Doré, C. J. and Newton, D. E. F. Effect of suxamethonium on the auditory evoked response in humans 34–37
Brunner, M. D., Thornton, C. and Newton, D. E. F. Suxamethonium and auditory evoked potentials, (*C*) 881
Brunner, M. D. *see* Shannon, C., (*C*) 472
Bryan, A., Pollard, B. J., Keegan, M. A. and Campbell, I. T. Post-tetanic constant stimulus train patterns during neuromuscular block with atracurium and vecuronium, (*ARS*) 579P
Buckland, M. *see* Turner, G. 606–610
Buggy, D. and MacDowell, C. Extradural analgesia in the first stage of labour, (*C*) 887
Buggy, D. J. and MacDowell, C. Extradural analgesia with clonidine and fentanyl compared with 0.25 % bupivacaine in the first stage of labour 319–321
Buhre, W., Schorn, B., Kazmaier, S., Weyland, A., Giannaris, S., Hoeft, A. and Sonntag, H. Assessment of right and left heart volume indices in patients undergoing coronary artery bypass surgery, (*EACTA*) A.37
Buhre, W. *see* Kazmaier, S., (*EACTA*) A.5
Bulder, E. R. *see* Jansen, P. G. M. 13–19
Bullingham, A. and Strunin, L. Venous thromboembolism and cardiovascular surgery, (*C*) 473
Bunting, H. E., Kelly, M. C. and Milligan, K. R. Nebulized lignocaine before gaseous induction with desflurane, (*C*) 596
Bureau, M. *see* Baele, Ph., (*EACTA*) A.60
Burm, A. G. L. *see* Boer, F. 203–208
Burns, T. *see* Dhond, G., (*EACTA*) A.57
Burrows, C. *see* Dhond, G., (*EACTA*) A.57
Busto, N. *see* López-Olaondo, L. 835–840
Buzello, W. *see* Nigrovic, V., (*ARS*) 580–581P

du Cailar, J. *see* Biboulet, P. 81–84
Calder, I. and Koh, K. F. Cervical haematoma and airway obstruction, (*C*) 888
Callesen, T. *see* Pedersen, J. L. 806–810
Calvert, B., Colson, P., Cuchet, D., Péastaing, M. and Wintrebert, P. Organ dysfunctions after cardiac surgery: definitions and prognosis, (*EACTA*) A.78
Çalýþýriþçi, Ü. *see* Toraman, F., (*EACTA*) A.21
Camann, W. Intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia, (*C*) 169
Campbell, C. E. *see* Cork, R. C. 492–498
Campbell, I. T. *see* Bryan, A., (*ARS*) 579P
Canik, S. *see* Özyurt, A., (*EACTA*) A.25; Toraman, F., (*EACTA*) A.21
Capdevila, X. *see* Biboulet, P. 81–84
Capouet, V., De Pauw, C., Vernet, B., Ivens, D., Derijcke, V., Versichelen, L., van Aken, H., Ickx, B., Ritter, L. and Hulstaert, F. Single dose i.v. tropisetron in the prevention of postoperative nausea and vomiting after gynaecological surgery 54–60
Cardan, E. *see* Gota, M., (*EACTA*) A.20; Vuylsteke, A., (*EACTA*) A.51
Carli, F. and Macdonald, I. A. Perioperative inadvertent hypothermia: what do we need to prevent? (*E*) 601–603
Carli, F. *see* West, M. R. J. 673–679
Carr , C. A. *see* Smith, G. B., (*R*) 891
Carrascosa, F. *see* López-Olaondo, L. 835–840
Carrie, L. E. S., Simpson, P. J. and Popat, M. T. *Understanding Anaesthesia*, 3rd Edn, (*R*) 892–893
Carroll, M., Day, F., Hennessy, A. and Cooney, C. Patient attitudes to perioperative suppository administration for postoperative analgesia, (*ARS*) 581P
Casati, V., Guzzon, D., Oppizzi, O., Tullii, M., Fiorucci, A., Venturino, M. and Paolillo, G. High dose aprotinin *vs* tranexamic acid in elective cardiac surgery: effects on bleeding and necessity of transfusion, (*EACTA*) A.53
Casey, W. *see* Lyons, B., (*ARS*) 589P
Caunt, J. A. *see* Ward, J. E. H., (*C*) 889
Chadd, G. D. *see* Newton, M. C. 352–357
Chamley, D. *see* Turner, G. 606–610
Champsaur, G. *see* Vedrinne, C., (*EACTA*) A.66
Chan, A. *see* Crabb, I. 795–801
Chantigian, R. C. *see* Southorn, P. 467–469
Chassard, D. *see* Tournadre, J. P. 130–132
Checketts, M. R., Gilhooly, C. J. and Kenny, G. N. C. Patient-maintained analgesia with alfentanil after cardiac surgery: a comparison with morphine PCA, (*EACTA*) A.69
Cheng, E. Y. *see* Mazzeo, A. J. 841–846
Cirri, S. *see* Ranucci, M., (*EACTA*) A.71
Clark, V. A. *see* Dunn, T. J., (*C*) 168
Clay, R. *see* Watt, J. W. H. 870–871
Clewlow, F. *see* Deakin, C. D., (*EACTA*) A.41
Cluitmans, P. J. M. *see* de Beer, N. A. M. 685–693
Cochran, D., Price, W. and Gwinnutt, C. L. Unilateral convulsion after induction of anaesthesia with propofol 570–572
Coddens, J., Deloof, T. and Housmans, P. Haemodynamic effects of sodium nitroprusside *versus* prostaglandin E_1 in heart transplant candidates, (*EACTA*) A.26
Coetzee, J. F., Maritz, J. S. and du Toit, J. C. Effect of tramadol on depth of anaesthesia 415–418
Cohen, P. J. *see* Healy, T. E. J., (*R*) 477
Collard, E. *see* Broka, S., (*EACTA*) A.44
Colquhoun, A. *see* Smith, E., (*EACTA*) A.86
Colquhoun, M. C., Handley, A. J. and Evans, T. R., (editors) *The ABC of Resuscitation*, 3rd Edn, (*R*) 338–339
Colson, P. *see* Calvert, B., (*EACTA*) A.78; Ryckwaert, F., (*EACTA*) A.34
Columb, M. O. *see* Murphy, P. G. 536–543
Consonni, F. *see* Fiacchino, F., (*C*) 883
Conti, D. *see* Ranucci, M., (*EACTA*) A.71
Conti, E. *see* Ranucci, M., (*EACTA*) A.71
Conti, J. and Smith, D. Haemodynamic effects of continued sedation during tracheal extubation, (*EACTA*) A.72
Conway, F. *see* Critchley, L. A. H. 734–736
Cook, B. and Doyle, E. Extradural clonidine for postoperative pain relief, (*C*) 881

Cook, L. B. *see* Smith, A. F., (*ARS*) 577P; Thorpe, S. J., (*ARS*) 576P
Coon, R. L. *see* Mazzeo, A. J. 841–846
Cooney, C. *see* Carroll, M., (*ARS*) 581P
Cooper, D. W., Ryall, D. M., McHardy, F. E., Lindsay, S. L. and Eldabe, S. S. Patient-controlled extradural analgesia with bupivacaine, fentanyl, or a mixture of both, after Caesarean section 611–615
Coppejans, H. C. *see* Vercauteren, M. P. 731–733
Corbett, A. *see* Eddleston, J. M. 66–71
Corbett, A. R. and Wisnewski, J. Use of regional i.v. morphine analgesia in patients undergoing total knee arthroplasty, (*ARS*) 593–594P
Coriat, P. *see* Langeron, O. 783–789
Cork, R. C., Heaton, J. F., Campbell, C. E. and Kihlstrom, J. F. Is there implicit memory after propofol sedation? 492–498
Cottam, S. and Milroy, S. J. Aprotinin during liver transplantation, (*C*) 882
Couture, P. *see* Langeron, O. 783–789
Crabb, I., Thornton, C., Konieczko, K. M., Chan, A., Aquilina, R., Frazer, N., Doré, C. J. and Newton, D. E. F. Remifentanil reduces auditory and somatosensory evoked responses during isoflurane anaesthesia in a dose-dependent manner 795–801
Critchley, L. A. H. and Conway, F. Hypotension during subarachnoid anaesthesia: haemodynamic effects of colloid and metaraminol 734–736
Crosby, G. *see* Goto, T. 702–706
Cross, M. *see* Daniell, C. J., (*ARS*) 586–587P
Cuchet, D. *see* Calvert, B., (*EACTA*) A.78
Cunningham, A. J., (editor) *Anaesthesia and Critical Care Manual*, 2nd Edn, (*R*) 338
Cunningham, A. J. *see* O'Leary, E. 640–644
Curatolo, M., Derighetti, M., Petersen-Felix, S., Feigenwinter, P., Fischer, M. and Zbinden, A. M. Fuzzy logic control of inspired isoflurane and oxygen concentrations using minimal flow anaesthesia 245–250
Curatolo, M., Orlando, A., Zbinden, A. M., Scaramozzino, P. and Venuti, F. S. A multifactorial analysis to explain inadequate surgical analgesia after extradural block, (*e*) 598
Curtil, A. *see* Vedrinne, C., (*EACTA*) A.66
Czapla, J. *see* Knapik, P., (*EACTA*) A.28

Daborn, A. K. *see* Phillips, S., (*C*) 471
Daŏsalý, S. *see* Özyurt, A., (*EACTA*) A.25
Daenen, W. *see* Herijgers, P., (*EACTA*) A.79; Meyns, B., (*EACTA*) A.38
Dahan, A. and Berkenbosch, A. Ventilatory response to carbon dioxide, (*C*) 747
Dahan, A., van Kleef, J., van den Elsen, M., Valk, R. and Berkenbosch, A. Slow ventilatory dynamics after isocapnic hypoxia and voluntary hyperventilation in humans: effects of isoflurane 374–381
Dahl, J. B. *see* Ilkjaer, S. 829–834
Dahlin, L. G., Lundberg, C., Kågedal, B., Nylander, E., Rutberg, H. and Svedjeholm, R. Troponin-T for asessment of myocardial damage in CABG surgery, (*EACTA*) A.62
Dahlin, L. G. *see* Svedjeholm, P., (*EACTA*) A.61
Dalmas, J. P. *see* Lehot, J. J., (*EACTA*) A.43
Dalmas, S., Marsch, S. C. U., Philbin, D. M., Gavaghan, D. J., Ryder, W. A. and Foëx, P. Effects and interactions of myocardial ischaemia and alterations in circulating blood volume on canine left ventricular diastolic function 419–427
Daniell, C. J., Cross, M., Sneyd, J. R., Thompson, P., Weideman, M. M. and Andrews, C. J. Org 21465 a new i.v. anaesthetic agent, (*ARS*) 586–587P
d'Athis, F. *see* Biboulet, P. 81–84
Davies, A. *see* Goodchild, C. S. 544–551
Davies, F. W. *see* Wolf, A. R. 362–364
Davies, M. J. *see* Murphy, P. G. 536–543
Davis, G., Khan, R. M., Randall, N., Wright, J. S. and Roberts, D. H. Balloon mitral valve dilatation as an aid to weaning from ventilatory support in patients with intractable pulmonary oedema caused by severe mitral stenosis 879–880
Dawson, P. *see* Turner, G. 606–610
Day, F. *see* Carroll, M., (*ARS*) 581P
Deakin, C. D. Evaluation of an oesophageal intubation detector device using electrical resistance, (*ARS*) 590P
Deakin, C. D., Sewell, A. C., Clewlow, F. and Pierce, J. M. T. A comparison of core temperature with thermal energy balance in predicting adequacy of rewarming from hypothermic cardiopulmonary bypass, (*EACTA*) A.41
DeBruyère, M. *see* Deneys, V., (*EACTA*) A.56
De Hert, S. G. *see* Deirue, G. L., (*EACTA*) A.10
Deirue, G. L., De Hert, S. G., Ten Broecke, P. W. and Vermeyen, K. M. Effects of lidoflazine on left ventricular function, (*EACTA*) A.10
Delhaas, E. M. Extradural and subarachnoid catheterization using the Seldinger technique 149–150
Delire, V. *see* Broka, S., (*EACTA*) A.44
Deloof, T. *see* Coddens, J., (*EACTA*) A.26
Delpy, D. T. *see* Owen-Reece, H. 43–48
Demeyere, R. *see* Meyns, B., (*EACTA*) A.38
Demirtaþ, M. *see* Toraman, F., (*EACTA*) A.21
Denda, S., Shimoji, K., Tomita, M., Baba, H., Yamakura, T., Masaki, H., Endoh, H. and Fukuda, S. Central nuclei and spinal pathways in feedback inhibitory spinal cord potentials in ketamine-anaesthetized rats 258–265
Deneys, V., VanDyck, M., DeBruyère, M., Waterloos, H. and Baele, Ph. Use of blood products in cardiovascular surgery 4 years after the Sanguis study, (*EACTA*) A.56
De Pauw, C. *see* Capouet, V. 54–60
Deplace, C. *see* Paulus, S., (*EACTA*) A.73
Derighetti, M. *see* Curatolo, M. 245–250
Derijcke, V. *see* Capouet, V. 54–60
De Wolf, A. M., Freeman, J. A., Scott, V. L., Tullock, W., Smith, D. A., Kisor, D. F., Kerls, S. and Ryan Cook, D. Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation 624–628
d'Hollander, A. *see* Nyarwaya, J.-B. 428–434
Dhond, G., Burns, T., Burrows, C., Wheeldon, D., Ghosh, S. and Oduro-Dominah, A. Pilot evaluation of RMI haemoconcentrator during cardiopulmonary bypass, (*EACTA*) A.57
D'hoore, W. *see* Baele, Ph., (*EACTA*) A.60
Dhoste, K. *see* Karayan, J. 459–460
Diemunsch, P. *see* Wilson, A. J. 515–518
Dijkhuis, J. P. *see* van der Stroom, J. G. 645–651
Dion, R. *see* Vuylsteke, A., (*EACTA*) A.50
Djaiani, G. N. *see* Knowles, P. R., (*EACTA*) A.42
Dockal, M. *see* Laßnigg, A., (*EACTA*) A.18
Dodds, C. *see* Rosenberg-Adamsen, S. 552–559
Dohmen, P. *see* Herijgers, P., (*EACTA*) A.13
Dolisi, C. *see* Raucoules-Aimé, M. 198–202
Domingo, V. *see* Aguilar, J. L. 72–76
Donatelli, F. *see* Guarracino, F., (*EACTA*) A.45
Donati, F. *see* Audibert, G., (*C*) 597–598
Döpfmer, S. *see* Döpfmer, U. R. 77–80
Döpfmer, U. R., Maloney, D. G., Gaynor, P. A., Ratcliffe, R. M. H. and Döpfmer, S. Prilocaine 3% is superior to a mixture of bupivacaine and lignocaine for peribulbar anaesthesia 77–80
Doran, B. R. H. *see* Pearson, A. J., (*ARS*) 577–578P
Doré, C. J. *see* Brunner, M. D. 34–37; Crabb, I. 795–801; Richmond, C. E. 446–448
Doyle, A. R. *see* Poulton, B. B., (*EACTA*) A.15
Doyle, E. *see* Cook, B., (*C*) 881; Semple, D. 310–312
Dresner, M. *see* Hawthorne, L. 680–684
Driver, I., Wiltshire, S., Mills, P., Lillywhite, N. and Howard-Griffin, R. Midazolam before induction improves conditions for laryngeal mask insertion, (*e*) 175
Drummond, G. B. Comparison of sedation with midazolam and ketamine: effects on airway muscle activity 663–667; Effect of apparatus on functional residual capacity 560–562
Drummond, G. B. *see* Foo, I. T. 214–220; Spens, H. J. 369–373; Sutherland, R. W. 777–779
Dryden, C. M. *see* Wolf, A. R. 362–364
Dubreuil, M. *see* Freyburger, G. 519–525
Ducart, A. *see* Broka, S., (*EACTA*) A.44
Dudea, S. *see* Gota, M., (*EACTA*) A.20
Du Gres, B. *see* Vedrinne, C., (*EACTA*) A.85
Dulcamara, A. *see* Fiacchino, F., (*C*) 883
Dunn, T. J., Clark, V. A. and Jones, G. Naproxen after day-case laparoscopic sterilization, (*C*) 168
Durand, P. G. *see* Vedrinne, C., (*EACTA*) A.85
Dursin, A. *see* Broka, S., (*EACTA*) A.44
Duthie, D. J. R. *see* Knowles, P. R., (*EACTA*) A.42; Poulton, B. B., (*EACTA*) A.15

Eastwood, N. B. *see* Boyd, A. H. 382–388
Eddleston, J. M., Holland, J. J., Griffin, R. P., Corbett, A., Horsman, E. L. and Reynolds, F. A double-blind comparison of 0.25% ropivacaine and 0.25% bupivacaine for extradural analgesia in labour 66–71
Ederberg, S., Ricksten, S-E., Svensson, S.-E. and Westerlind, A. The effects of propofol on cerebral blood flow velocity and oxygenation during cardiopulmonary bypass, (*EACTA*) A.17
Edwards, N. D. *see* Mason, D. G. 396–400
Eggensperger, N. *see* Walpoth, B. H., (*EACTA*) A.58
van Egmond, J. *see* Vanlinthout, L. E. H. 389–395

Ehrlich, M. *see* Laßnigg, A., (*EACTA*) A.18

Eijsman, L. *see* Jansen, P. G. M. 13–19

Ekberg, K. *see* Gårdebäck, M., (*EACTA*) A.36

El-Bakry, A. K. *see* Naguib, M., (*e*) 339

Eldabe, S. S. *see* Cooper, D. W. 611–615

Elkhoury, Z. *see* Molliex, S. 151–153

Elliott, D. W., Voyvodic, F. and Brownridge, P. Sudden onset of subarachnoid block after subdural catheterization: a case of arachnoid rupture? 322–324

van den Elsen, M. *see* Dahan, A. 374–381

Elwell, C. E. *see* Owen-Reece, H. 43–48

Endoh, H. *see* Denda, S. 258–265

Engberg, G. *see* Reber, A. 760–766

England, A. J., Richards, K. and Feldman, S. A. Effect of cooling on the force of contraction of rat and guineapig phrenic nerve hemidiaphragm preparations, (*ARS*) 592–593P

England, A. J. *see* Richards, K., (*ARS*) 579–580P

Enright, S. and Bellamy, M. C. White blood cell cytosolic calcium changes during human orthotopic liver transplantation, (*ARS*) 587–588P

Enright, S. *see* Snook, N. J. 740–743

Erdemir, H. *see* Özyurt, A., (*EACTA*) A.25

Espachs, P. *see* Aguilar, J. L. 72–76

Espinet, A., Henderson, D. J., Faccenda, K. A. and Morrison, L. M. M. Does pre-incisional thoracic extradural block combined with diclofenac reduce postoperative pain after abdominal hysterectomy? 209–213

Evans, M. J., Harrison, C. A. and Mapleson, W. W. A pitfall in the use of the Altman nomogram for power estimation, (*C*) 334

Evans, S. J. W. *see* Toner, C. C. 347–351

Evans, T. R. *see* Colquhoun, M. C., (*R*) 338–339

Faccenda, K. A. *see* Espinet, A. 209–213

Fairfield, M. C. Visceral pain during Caesarean section, (*C*) 167

Farmery, A. D. and Roe, P. G. A model to describe the rate of oxyhaemoglobin desaturation during apnoea 284–291; A model to describe the rate of oxyhaemoglobin desaturation during apnoea, (*e*) 890

Farrell, P. T. Suxamethonium in children, (*C*) 883–884

Favre, H. *see* Licker, M. 632–639

Fee, J. P. H. *see* Gormley, W. P. 802–805

Feigenwinter, P. *see* Curatolo, M. 245–250

Feldman, A. *see* Richards, K., (*ARS*) 579–580P

Feldman, S. *Neuromuscular Block*, (*R*) 893

Feldman, S. and Hood, J. Factors governing onset of neuromuscular block, (*C*) 596–597

Feldman, S. A. *see* England, A. J., (*ARS*) 592–593P

Feneck, R. *see* Vuylsteke, A., (*EACTA*) A.30; (*EACTA*) A.77

Ferdinande, P. *see* Meyns, B., (*EACTA*) A.38

Fernando, R. and Parry, M. G. Extradural analgesia in the first stage of labour, (*C*) 886–887

Fernando, R. *see* Robbins, P. M., (*C*) 170

Ferrante, M. *see* Paino, R., (*EACTA*) A.40

Fiacchino, F., Consonni, F., Dulcamara, A. and Grandi, L. Suxamethonium in children, (*C*) 883

Filley, S., Bonnefoy, E., Blanc, P., Bouvier, H., Guidollet, J. and Lehot, J. J. Time course of serial serum troponin I levels after coronary artery bypass surgery (CABG), (*EACTA*) A.63

Findlay, G. P. and Spittal, M. J. Rocuronium pretreatment reduces suxamethonium-induced myalgia: comparison with vecuronium 526–529

Fink, E. J. jr and Brown, B. B. jr, (editors) *Baillière's Clinical Anaesthesiology: New Pharmacological Vistas*, (*R*) 173

Fiorucci, A. *see* Casati, V., (*EACTA*) A.53

Fischer, M. *see* Curatolo, M. 245–250; Roth, D. 38–42

Flameng, W. *see* Herijgers, P., (*EACTA*) A.13; (*EACTA*) A.14; (*EACTA*) A.79; Meyns, B., (*EACTA*) A.38

Flamens, C. *see* Lehot, J. J., (*EACTA*) A.43; Paulus, S., (*EACTA*) A.73

Fleming, B. G. *see* Munglani, R., (*E*) 1–4

Fletcher, G. C., Asbury, A. J. and Brown, J. H. Pupil changes during cardiopulmonary bypass 20–22

Fletcher, S. J. *see* Heath, K. J. 877–878

Foëx, P. *see* Dalmas, S. 419–427

Folliguet, T. *see* Pétrie, J., (*EACTA*) A.54

Foo, I. T., Warren, P. M. and Drummond, G. B. Influence of oral clonidine on the ventilatory response to acute and sustained isocapnic hypoxia in human males 214–220

Ford, S. *see* Price, C. M. 464–466

Forse, R. A. *see* Tellado, J. M., (*R*) 173–174

Foster, R. N. Effect of transdermal hyoscine on nausea and vomiting, (*C*) 749

Fothergill, J. *see* Secker, C., (*ARS*) 581–582P

Fourie, J. *see* James, M. F. M. 713–720

Fox, A. and Mushambi, M. C. Accidental insertion of an extradural catheter, (*C*) 336

Franco, A. *see* Oppizzi, M., (*EACTA*) A.46

Franks, R. *see* Karmakar, M. K. 811–815

Fraser, M. H. *see* Watt, J. W. H. 870–871

Frazer, N. *see* Crabb, I. 795–801

Freeman, J. A. *see* De Wolf, A. M. 624–628

Frey, L. *see* Welte, M. 90–98

Freyburger, G., Dubreuil, M., Boisseau, M. R. and Janvier, G. Rheological properties of commonly used plasma substitutes during preoperative normovolaemic acute haemodilution 519–525

Fruhwald, F. M. *see* Fruhwald, S., (*EACTA*) A.65

Fruhwald, S., Fruhwald, F. M., Gütl, M. and Metzler, H. QTc-dispersion in patients undergoing CABG surgery, (*EACTA*) A.65

Fuchs-Buder, T. and Tassonyi, E. Magnesium sulphate enhances residual neuromuscular block induced by vecuronium 565–566

Fukuda, H. *see* Hirabayashi, Y., (*C*) 167; 508–510; (*C*) 886

Fukuda, S. *see* Denda, S. 258–265

Fukushima, T., Hirasaki, A., Jones, K. A. and Warner, D. O. Halothane and potassium channels in airway smooth muscle 847–853

Furuse, M. *see* Hirabayashi, Y. 508–510

Fusciardi, J. *see* Karayan, J. 459–460

Gajraj, N. M. and Hutter, C. Serotonin in pre-eclampsia, (*C*) 748–749

Galletly, D. C., Williams, T. B. and Robinson, B. J. Periodic cardiovascular and ventilatory activity during midazolam sedation 503–507

Galley, H. F. *see* Pittard, A. J. 629–631

Gårdebäck, M., Settergren, G., Wahren, J., Ekberg, K. and Barr, G. Splanchnic blood flow during cardiopulmonary bypass assessed by indicator dilution technique, (*EACTA*) A.36

Garraffo, R. *see* Isetta, C., (*EACTA*) A.52

Gastaud, P. *see* Raucoules-Aimé, M. 198–202

Gavaghan, D. J. *see* Dalmas, S. 419–427

Gaynor, P. A. *see* Döpfmer, U. R. 77–80

Geerts, M. *see* Boer, F. 203–208

Gelinder, S., Orre, L., Settergren, G., Samuelson, S. and Norman, M. Stable right ventricular pressure-volume relation during lung volume reducing surgery for diffuse emphysema, (*EACTA*) A.80

Gent, J. P. *see* Goodchild, C. S. 544–551

Gentili, M. and Bonnet, F. Spinal clonidine produces less urinary retention than spinal morphine 872–873

George, M. *see* Vedrinne, C., (*EACTA*) A.85

George, S. J. Transoesophageal echocardiography in chest trauma, (*C*) 336–337

Gerli, C. *see* Oppizzi, M., (*EACTA*) A.81

Gersbach, Ph. *see* Walpoth, B. H., (*EACTA*) A.7

Geskes, G. *see* Pietersen, H. G., (*EACTA*) A.2

Ghosh, S. *see* Dhond, G., (*EACTA*) A.57

Giannaris, S. *see* Buhre, W., (*EACTA*) A.37

Gilhooly, C. J. *see* Checketts, M. R., (*EACTA*) A.69

Gillon, K. R. W. *see* Levack, I. D. 567–569

Ginsburg, R. *see* Kaufman, L., (*R*) 174

Glynn, C. J. *see* Souter, A. J., (*C*) 595–596

Goldstone, J. *see* Owen-Reece, H. 43–48

Goodchild, C. *see* Turner, G. 606–610

Goodchild, C. S., Guo, Z., Davies, A. and Gent, J. P. Antinociceptive actions of intrathecal xylazine: interactions with spinal cord opioid pathways 544–551

Goodman, N. W. Measurement of competence, (*C*) 750

Goodman, N. W. and Johnson, C. *600 MCQs in Anaesthesia: Clinical Practice*, 2nd Edn, (*R*) 751

Goodyer, P. *see* Secker, C., (*ARS*) 581–582P

Goold, J. E. Day-case cataract surgery, (*C*) 333

Gopinath, S. *see* Knowles, P. R., (*EACTA*) A.42

Gorchein, A. Porphyria, propofol and rats, (*C*) 172

Gormley, W. P., Murray, J. M., Fee, J. P. H. and Bower, S. Effect of the addition of alfentanil to lignocaine during axillary brachial plexus anaesthesia 802–805

Gosling, A. J. *see* Sabar, M. A., (*ARS*) 584P

Gota, M., Dudea, S., Sandor, V., Knowles, P., Latimer, R. D. and Cardan, E. Topical nitroglycerin dilates the radial artery, (*EACTA*) A.20

Goto, T., Marota, J. J. A. and Crosby, G. Volatile anaesthetics antagonize nitrous oxide and morphine-induced analgesia in the rat 702–706

Gouwy, S., Wouters, P., Verhamme, B., Vebruggen, W. and Lauwers, P. Autotransfusion of unwashed shed blood after

CABG, using the Atrium 2052® blood recovery system, (*EACTA*) A.59
Graham, D. and Kaddour, H. S. RAE tube obstruction during tonsil dissection, (*C*) 170–171
Grandi, L. *see* Fiacchino, F., (*C*) 883
Grebenik, C. and Allman, C. Nausea and vomiting after cardiac surgery, (*EACTA*) A.76
Greiff, J. *see* Thompson, M. M., (*C*) 883
Griffin, R. P. *see* Eddleston, J. M. 66–71
Grimaud, D. *see* Isetta, C., (*EACTA*) A.52; Raucoules-Aimé, M. 198–202
Groh, J. *see* Welte, M. 90–98
Grossi, A. *see* Guarracino, F., (*EACTA*) A.45
Grouls, R. J. E. *see* de Beer, N. A. M. 685–693
Grounds, R. M. *see* Boyd, O., (*C*) 598; (*C*) 750
Grüne, F. *see* Weyland, A., (*EACTA*) A.35
Guarracino, F., Oppizzi, M., Triggiani, M., Benussi, S., Donatelli, F., Paolillo, G. and Grossi, A. Transoesophageal echocardiography and haemodynamic monitoring in emergency surgical revascularization for extensive acute myocardial infarction, (*EACTA*) A.45
Guarracino, F. *see* Oppizzi, M., (*EACTA*) A.46; (*EACTA*) A.81
Guerit, J. M. *see* Vuylsteke, A., (*EACTA*) A.50
Guidollet, J. *see* Filley, S., (*EACTA*) A.63
Guillou, P. J. *see* Bellamy, M. C., (*ARS*) 587P
Gunawardana, R. H. Difficult laryngoscopy in cleft lip and palate surgery 757–759
Günnicker, M. *see* Karzai, W. 5–8
Guo, Z. *see* Goodchild, C. S. 544–551
Gürtler, C. *see* Reber, A., (*ARS*) 584P
Gütl, M. *see* Fruhwald, S., (*EACTA*) A.65
Guzzon, D. *see* Casati, V., (*EACTA*) A.53
Gwinnutt, C. L. *see* Cochran, D. 570–572
Gyi, A. *see* Selwyn, D. A. 111–115

Hägglöf, B. *see* Schug, S. A. 487–491
Hagon, O. *see* Wilder-Smith, O. H. G., (*C*) 472–473
Hahn, M. B., McQuillan, P. M. and Sheplock, G. J., (editors) *Regional Anesthesia: An Atlas of Anatomy and Techniques*, (*R*) 751
Hahn, R. G. *see* Olsson, J. 85–89
Haider, W. *see* Mares, P., (*EACTA*) A.75; Rajek, A., (*EACTA*) A.39
Hak, A. *see* Boer, F. 203–208
Håkanson, E., Szabo, Z., Svedjeholm, R., Lindahl, M. and Tagesson, C. Phospholipase A_2 in cardiac surgery, (*EACTA*) A.1
Hall, G. M. *see* Newton, M. C. 352–357
Hall, J. L. *see* Myles, P. S. 694–698
Hall, L. W. *see* Poulton, B. B., (*EACTA*) A.29
Haller, M. *see* Welte, M. 90–98
Halligan, A. W. *see* Mushambi, M. C. 133–148; (*C*) 889–890
Hamilton, R. C. *see* Maltby, J. R., (*C*) 333; Smith, G. B., (*R*) 891
Hammarén, E., Yli-Hankala, A., Rosenberg, P. and Hynynen, M. Plasma concentration and protein binding of propofol during cardiac surgery, (*EACTA*) A.16
Hammond, E. J. *see* McIndoe, A. K., (*C*) 332–333
Hancock, L. *A Physicians's Guide to the Internet*, (*R*) 893
Handley, A. J. *see* Colquhoun, M. C., (*R*) 338–339
Hann, H. C. L. and Raphael, J. H. Investigation into the effects of midazolam and propofol on human respiratory cilia beat frequency *in vitro*, (*ARS*) 591P
Hann, H. C. L. *see* Raphael, J. H. 854–859
Hanning, C. D. *see* Secker, C., (*ARS*) 581–582P
Hansson, L.-O. *see* van der Linden, J., (*EACTA*) A.84
Haraldsson, Å., Kieler-Jensen, N., Nathorst-Westfelt, U., Bergh, C.-H. and Ricksten, S.-E. Inhaled prostacyclin compared to inhaled nitric oxide in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance, (*EACTA*) A.27
Harkness, W. *see* Owen-Reece, H. 43–48
Harkness, W. F. J. *see* Smith, M. 499–502
Harmand, M. F. *see* Briquet, F., (*EACTA*) A.31
Harrison, C. A. *see* Evans, M. J., (*C*) 334
Harrison, M. J. G. *see* Arowsmith, J. E., (*EACTA*) A.83
Harrison, S. J. and Ponte, J. Convective warming combined with vasodilator therapy accelerates core rewarming after coronary artery bypass surgery 511–514
Hartiala, J. *see* Kentala, E., (*EACTA*) A.64
Hatch, D. J. Airway management in cleft lip and palate surgery, (*E*) 755–756
Hatch, D. J. *see* Phillips, S., (*C*) 471
Hawthorne, L., Wilson, R., Lyons, G. and Dresner, M. Failed intubation revisited: 17-yr experience in a teaching maternity unit 680–684
Healy, T. E. J. and Cohen, P. J., (editors) *Wylie & Churchill-Davidson's A Practice of Anaesthesia*, 6th Edn. (*R*) 477
Healy, T. E. J. and Pomfrett, C. J. D. Isolated forearm technique, (*C*) 885–886
Heath, K. J., Palmer, M. and Fletcher, S. J. Fracture of the cricoid cartilage after Sellick's manoeuvre 877–878
Heath, M. *see* Thomas, V. J., (*C*) 595
Heaton, B. *see* McGowan, C. 868–869
Heaton, J. F. *see* Cork, R. C. 492–498
Hechema, R. *see* Isetta, C., (*EACTA*) A.52
Hedenstierna, G. *see* Reber, A. 760–766
Heine, J. F. *see* Leuwer, M., (*ARS*) 585P
Helbo-Hansen, H. S. *see* Wilson, A. J. 515–518
Helminen, A. *see* Kentala, E., (*EACTA*) A.64
Henderson, D. J. *see* Espinet, A. 209–213
Henderson, J. D. *see* Ireland, N. 657–662
Hendrata, M. *see* Myles, P. S. 694–698; Turner, G. 606–610
Hennessy, A. *see* Carroll, M., (*ARS*) 581P
Hensley, F. A. jr and Martin, D. E., (editors) *A Practical Approach to Cardiac Anesthesia*, (*R*) 174
Herijgers, P., Mubagwa, K., Dohmen, P. and Flameng, W. Brain death induced haemodynamic failure in the rat is solely due to autonomic denervation, (*EACTA*) A.13
Herijgers, P., Nishimura, Y. and Flameng, W. Serotonin induces coronary spasms after brain death in dogs, (*EACTA*) A.14
Herijgers, P., Szécsi, J., Daenen, W., Sergeant, P. and Flameng, W. Use of internal mammary artery improves prognosis in patients under 70 undergoing combined valve and coronary artery surgery, (*EACTA*) A.79
Heriot, J. A., Steven, C. M. and Sattin, R. S. Elective forceps delivery and extradural anaesthesia in a primigravida with portal hypertension and oesophageal varices 325–327
Herity, N. A. *see* Allen, J. D., (*E*) 177–178
Hett, D., Pilkington, S., Janke, E., Sheppard, S. and Smith, D. Blood lactate during cardiopulmonary bypass with a lactated priming solution, (*EACTA*) A.33
Hickman, R. *see* James, M. F. M. 713–720
Hiesmayr, M., Spittler, A., Laßnigg, A., Berger, R., Boltz, G. and Roth, E. Perioperative changes in receptors for ICAM-1/CD54 and immunglobulin G on monocytes by extracorporeal circulation (ECC), (*EACTA*) A.32
Hiesmayr, M. *see* Laßnigg, A., (*EACTA*) A.18; Mares, P., (*EACTA*) A.75; Rajek, A., (*EACTA*) A.39
Hind, C. J. and Watson., D. *Intensive Care: A Concise Textbook*, 2nd Edn, (*R*) 599
Hirabayashi, Y., Saitoh, K., Fukuda, H. and Shimizu, R. Visceral pain during Caesarean section, (*C*) 167
Hirabayashi, Y., Shimizu, R., Saitoh, K. and Fukuda, H. CSF progesterone concentrations in pregnancy, (*C*) 886
Hirabayashi, Y., Shimizu, R., Saitoh, K., Fukuda, H., Igarashi, T. and Furuse, M. Anatomical configuration of the spinal column in the supine position. III. Comparison of adolescent and adult volunteers 508–510
Hirabayashi, Y. *see* Ikeno, S. 573–575
Hirasaki, A. *see* Fukushima, T. 847–853
Hirota, K. and Lambert, D. G. Is the dihydropyridine binding site on neuronal L-type calcium channels a target for i.v. anaesthetic agents? (*ARS*) 591P; Voltage-sensitive Ca^{2+} channels and anaesthesia, (*E*) 344–346
Hirota, K., Sato, T., Rabito, S. F., Zsigmond, E. K. and Matsuki, A. Relaxant effect of ketamine and its isomers on histamine-induced contraction of tracheal smooth muscle 266–270
Hobbhahn, J. *see* Rödig, G. 9–12
Hodges, U. M. Vecuronium infusion requirements in paediatric patients in intensive care units: the use of acceleromyography 23–28
Hoeft, A. *see* Buhre, W., (*EACTA*) A.37; Mielck, F., (*EACTA*) A.12
Hoffmann, V. *see* Vercauteren, M. P. 731–733
Hohn, L. *see* Schweizer, A., (*EACTA*) A.55
Holland, J. J. *see* Eddleston, J. M. 66–71
Hollmann, M. *see* Schlack, W. 860–867
Homi, J. *see* West, M. E., (*C*) 167
Honkavaara, P. Effect of ondansetron on nausea and vomiting after middle ear surgery during general anaesthesia 316–318; Effect of transdermal hyoscine on nausea and vomiting, (*C*) 749–750; Effect of transdermal hyoscine on nausea and vomiting during and after middle ear surgery under local anaesthesia 49–53
Honkonen, E. L., Kaukinen, L., Pehkonen, E. J. and Kaukinen, S. Atrial natriuretic peptide (ANP) and N-terminal ANP: relationship to right ventricular function in patients undergoing coronary artery bypass surgery, (*EACTA*) A.6
Hood, J. *see* Feldman, S., (*C*) 596–597

van Hooff, J. C. *see* de Beer, N. A. M. 685–693
Hopkins, P. M. Suxamethonium in children, (*C*) 884
Hopp, M. Preoperative fasting for paediatric anaesthesia, (*C*) 471
Horsman, E. L. *see* Eddleston, J. M. 66–71
Horton, R. C. *see* Kendall, M. J., (*R*) 891–892
Housmans, P. *see* Coddens, J., (*EACTA*) A.26
Howard-Griffin, R. *see* Driver, I., (*e*) 175
Hubbard, K. *see* O'Leary, E. 640–644
Huber, P. R. *see* Reber, A., (*ARS*) 584P
Hughes, D. *see* Thomas, D. G. 61–65; Tremlett, M. R., (*ARS*) 583–584P
Hughes, D. G., Mather, S. J. and Wolf, A. R., (editors) *Handbook of Neonatal Anaesthesia*, (*R*) 599
Hughes, P. *see* Mayor, A. H., (*ARS*) 578–579P
Hulstaert, F. *see* Capouet, V. 54–60
Hunt, S. P. *see* Munglani, R., (*E*) 1–4
Hunter, J. M. Rocuronium: the newest aminosteroid neuromuscular blocking drug, (*E*) 481–483
Hunter, J. M. *see* Boyd, A. H. 382–388
Hutter, C. *see* Gajraj, N. M., (*C*) 748–749
Hutter, C. D. D. Maternal sequelae of childbirth, (*C*) 474
Hutton, P. *see* Benson, J. P., (*C*) 472
Huybregts, M. A. J.M. *see* Jansen, P. G. M. 13–19
Hynynen, M. *see* Hammarén, E., (*EACTA*) A.16

Ickx, B. *see* Capouet, V. 54–60
Igarashi, T. *see* Hirabayashi, Y. 508–510
Ikeda, K. *see* Kazama, T. 530–535
Ikeno, S., Mitsuhata, H., Saito, K., Hirabayashi, Y., Akazawa, S., Kasuda, H. and Shimizu, R. Airway management for patients with a tracheal bronchus 573–575
Ilic, V. *see* Jovic, M., (*EACTA*) A.49
Ilkjaer, S., Petersen, K. L., Brennum, J., Wernberg, M. and Dahl, J. B. Effect of systemic *N*-methyl-D-aspartate receptor antagonist (ketamine) on primary and secondary hyperalgesia in humans 829–834
Ireland, M. *see* Kennedy, N., (*C*) 337
Ireland, N., Meagher, J., Sleigh, J. W. and Henderson, J. D. Heart rate variability in patients recovering from general anaesthesia 657–662
Isetta, C., Garraffo, R., Merville, C., Lugrin, D., Hechema, R., Sanchez, B., Jourdan, J. and Grimaud, D. Plasma levels of tranexamic acid after two injections during cardiac surgery with cardiopulmonary bypass, (*EACTA*) A.52
Isetta, C. *see* Briquet, F., (*EACTA*) A.31
Ivens, D. *see* Capouet, V. 54–60

Jadoul, J. L. and Jamaer, Ph. Comparison of sotalol and digoxin in the prevention of early supraventricular arrhythmias after coronary artery bypass graft (CABG), (*EACTA*) A.67
Jäger, K. *see* Leuwer, M., (*ARS*) 585P
Jalonen, J. *see* Kentala, E., (*EACTA*) A.64
Jamaer, Ph. *see* Jadoul, J. L., (*EACTA*) A.67
James, K. S. *see* Mansfield, M. D. 358–361
James, M. F. M., Hickman, R., Janicki, P., Mets, B. and Fourie, J. Early effects of total hepatectomy on haemodynamic state and organ uptake of catecholamines in the pig 713–720
James, M. F. M. *see* Ruttmann, T. G. 412–414
Janicki, P. *see* James, M. F. M. 713–720
Janke, E. *see* Hett, D., (*EACTA*) A.33
Jansen, P. G. M., te Velthuis, H., Wildevuur, W. R., Huybregts, M. A. J.M., Bulder, E. R., van der Spoel, H. I., Sturk, A., Eijsman, L. and Wildevuur, C. R. H. Cardiopulmonary bypass with modified fluid gelatin and heparin-coated circuits 13–19
Janvier, G. *see* Freyburger, G. 519–525
Jauch, K.-W. *see* Welte, M. 90–98
Jenni, R. *see* Schmidlin, D., (*EACTA*) A.48
Johnson, C. *see* Goodman, N. W., (*R*) 751
Johnston, K. R., Vickers, M. D. and Mapleson, W. W. Comparison of arterialized venous with arterial blood propofol concentrations during sub-anaesthetic infusions in volunteers 401–404
Jolin-Mellgård, Å. *see* Vuylsteke, A., (*EACTA*) A.30; (*EACTA*) A.77
Jonas, M. M. *see* West, M. R. J. 673–679
Jones, G. *see* Dunn, T. J., (*C*) 168
Jones, K. A. *see* Fukushima, T. 847–853
Jones, N. B. *see* Secker, C., (*ARS*) 581–582P
Jornod, N. *see* Schweizer, A., (*EACTA*) A.55
Joucken, K. *see* Broka, S., (*EACTA*) A.44
Jouppila, P. *see* Karinen, J. 616–620
Jouppila, R. *see* Karinen, J. 616–620
Jourdan, J. *see* Isetta, C., (*EACTA*) A.52
Jovic, M., Popovic, Z., Radomir, B., Ilic, V., Panic, G., Bojic, M., Popivic, A. and Babic, M. Transoesophageal echocardiography and intraoperative evaluation of left ventricular performance, (*EACTA*) A.49
Joyce, C. J., Baker, A. B., Parkinson, R. and Zacharias, M. Nitrous oxide and the rate of gas uptake from an unventilated lung in dogs 292–296

Kaddour, H. S. *see* Graham, D., (*C*) 170–171
Kågedal, B. *see* Dahlin, L. G., (*EACTA*) A.62
Kal, J. E. *see* van der Stroom, J. G. 645–651
Kalangos, A. *see* Schweizer, A., (*EACTA*) A.55
Kaliœ, R. *see* Knapik, P., (*EACTA*) A.28
Kamitani, K. Effects of propofol on rabbit mesenteric arteries and veins, (*C*) 333–334
Kampine, J. P. *see* Mazzeo, A. J. 841–846
Kang, Y. *see* Park, G. R., (*R*) 338
Kanmura, Y. *see* Tsuneyoshi, I. 251–257
Kaplan, N. M. *see* Kendall, M. J., (*R*) 891–892
Karayan, J., Thomas, D., Lacoste, L., Dhoste, K., Ricco, J. B. and Fusciardi, J. Delayed forced air warming prevents hypothermia during abdominal aortic surgery 459–460
Karevold, A. *see* Kirkeby-Garstad, I., (*EACTA*) A.74
Karinen, J., Räsänen, J., Alahuhta, S., Jouppila, R. and Jouppila, P. Maternal and uteroplacental haemodynamic state in pre-eclamptic patients during spinal anaesthesia for Caesarean section 616–620
Karmakar, M. K., Booker, P. D., Franks, R. and Pozzi, M. Continuous extrapleural paravertebral infusion of bupivacaine for post-thoracotomy analgesia in young infants 811–815
Karzai, W., Lötte, A., Günnicker, M., Vorgrimler-Karzai, U. M. and Priebe, H.-J. Dobutamine increases oxygen consumption during constant flow cardiopulmonary bypass 5–8
Kasuda, H. *see* Ikeno, S. 573–575
Kato, T. *see* Kazama, T. 530–535
Kaufman, L. and Ginsburg, R., (editors) *Anaesthesia: Review 11*, (*R*) 174
Kaukinen, L. *see* Honkonen, E. L., (*EACTA*) A.6
Kaukinen, S. *see* Honkonen, E. L., (*EACTA*) A.6
Kazama, T., Ikeda, K., Kato, T. and Kikura, M. Carbon dioxide output in laparoscopic cholecystectomy 530–535
Kazmaier, S., Buhre, W., Weyland, A., Stephan, H., Züchner, K. and Sonntag, H. Experimental evaluation of a single breath inert gas technique for measurement of myocardial blood flow, (*EACTA*) A.5
Kazmaier, S. *see* Buhre, W., (*EACTA*) A.37; Weyland, A., (*EACTA*) A.35
Keegan, M. A. *see* Bryan, A., (*ARS*) 579P
Kehlet, H. *see* Pedersen, J. L. 806–810; Rosenberg-Adamsen, S. 552–559
Kelly, M. C. *see* Bunting, H. E., (*C*) 596
Kendall, M. J., Kaplan, N. M. and Horton, R. C., (editors) *Difficult Hypertension: Practical Management and Decision Making*, (*R*) 891–892
Kennedy, N. and Ireland, M. Transoesophageal echocardiography in chest trauma, (*C*) 337
Kenny, G. N. C. *see* Checketts, M. R., (*EACTA*) A.69
Kentala, E., Hartiala, J., Helminen, A., Jalonen, J., Sariola-Heinonen, K., Virtanen, T. and Scheinin, H. Myocardial ischaemia and heart rate variability after coronary bypass surgery, (*EACTA*) A.64
Kerls, S. *see* De Wolf, A. M. 624–628
Kestin, I. G. *see* Montgomery, J. E., (*ARS*) 591–592P
Key, A. *see* Selwyn, D. A. 111–115
Keyl, C. *see* Rödig, G. 9–12
Khan, R. M. *see* Davis, G. 879–880
Khan, Z. *see* Reber, A., (*ARS*) 584P
Kieler-Jensen, N. *see* Haraldsson, Å., (*EACTA*) A.27
Kihlstrom, J. F. *see* Cork, R. C. 492–498
Kikura, M. *see* Kazama, T. 530–535
Kinsella, J. *see* Mansfield, M. D. 358–361
Kirby, F. *see* Lyons, B., (*ARS*) 589P
Kirkeby-Garstad, I., Sellevold, O. F. M. and Karevold, A. Oxygen consumption during early mobilization after CABG surgery in patients with normal cardiac function, (*EACTA*) A.74
Kirkham, A. J. T. *see* Poulton, B. B., (*EACTA*) A.15
Kisor, D. F. *see* De Wolf, A. M. 624–628
Kitching, A. J., Walpole, A. R. and Blogg, C. E. Removal of the laryngeal mask airway in children: anaesthetized compared with awake 874–876
van Kleef, J. *see* Dahan, A. 374–381
Kleinjans, H. A. J. *see* van der Stroom, J. G. 645–651
Klepetko, W. *see* Mares, P., (*EACTA*) A.75

Knapik, P., Wojtalik, M., Czapla, J., Kalice, R. and Nadziakiewicz, P. Correlation of predicted and recorded concentrations of nitric oxide during long-term inhalation in infants after cardiac surgery, (*EACTA*) A.28

Knill-Janes, R. P. *see* Maran, N. J., (*ARS*) 581P

Knos, G. B. *see* Berry, A. J., (*R*) 891

Knowles, P. *see* Gota, M., (*EACTA*) A.20

Knowles, P. R., Moshal, D. C., Djaiani, G. N., Gopinath, S. and Duthie, D. J. R. Convective warming overcomes effects of cooling after cardiopulmonary bypass, (*EACTA*) A.42

Koh, K. F. *see* Calder, I., (*C*) 888

Kong, K. L. *see* Wilson, A. J. 515–518

Konieczko, K. M. *see* Crabb, I. 795–801; Nathwani, D., (*ARS*) 589P

Koolen, J. J. *see* van der Stroom, J. G. 645–651

Kopman, E. *see* Özyurt, A., (*EACTA*) A.25

Kopman, E. A. *see* Toraman, F., (*EACTA*) A.21

Korpela, R. *see* Meretoja, O. A. 767–771

Korsten, H. H. M. *see* de Beer, N. A. M. 685–693

Kosaka, Y. *see* Saito, Y., (*C*) 747–748

Kroeks, M. V. A.M. *see* Wilson, A. J. 515–518

Krug, A. *see* Brase, R., (*EACTA*) A.47

Kuckelt, W. *see* Brase, R., (*EACTA*) A.47

Kuitunen, A. H. *see* Niemi, T. T. 822–828

Kulkarni, V., McFarlane, H. and Webster, N. R. Pulmonary lactate flux after cardiopulmonary bypass, (*ARS*) 586P

Kupilik, N. *see* Rajek, A., (*EACTA*) A.39

Kurata, J., Adachi, T., Nakao, S., Murakawa, M., Shichino, T., Shibata, M. and Mori, K. Sevoflurane, enflurane and isoflurane have no persistent postanaesthetic effects on the central nervous system in cats 721–725

Kurth, G. *see* Walpoth, B. H., (*EACTA*) A.58

Kviele, L. *see* Reber, A. 760–766

Kwan, W.-F. *see* Lee, C. 278–283

Kyttä, J., Randell, T. and Tanskanen, P. Venous air embolism: is end-tidal oxygen monitoring more informative than end-tidal carbon dioxide? (*C*) 475–476

Labib, Y. *see* Raucoules-Aimé, M. 198–202

Lacoste, L. *see* Karayan, J. 459–460

Lambert, D. G. *see* Appadu, B. L. 271–273; Hirota, K., (*E*) 344–346; (*ARS*) 591P; Selwyn, D. A. 274–277; Wandless, A. L. 461–463

Lampert, R., Rudlof, B. and Rauscher, J. The influence of dopaminergic agents on liver venous and mixed venous O_2-saturation in MODS – a preliminary report, (*EACTA*) A.11

de Lange, S. *see* Pietersen, H. G., (*EACTA*) A.2; Weterings, C. J., (*EACTA*) A.8; Willigers, H. M. M., (*EACTA*) A.23

Langenberg, C. J. M. *see* Pietersen, H. G., (*EACTA*) A.2

Langeron, O., Couture, P., Mateo, J., Riou, B., Pansard, J.-L. and Coriat, P. Oxygen consumption and delivery relationship in brain-dead organ donors 783–789

Langton, J. A. *see* Raphael, J. H. 116–121; 854–859; Selwyn, D. A. 111–115; 274–277

Lanz, M. *see* Walpoth, B. H., (*EACTA*) A.58

Laorden, M. L. *see* Llobel, F. 106–110

Laßnigg, A., Spittler, A., Marx, E., Bacher, A., Dockal, M., Ehrlich, M., Roth, E. and Hiesmayr, M. Does propofol change the phenotype of monocytes in thoracic surgery? (*EACTA*) A.18

Laßnigg, A. *see* Hiesmayr, M., (*EACTA*) A.32; Mares, P., (*EACTA*) A.75

Latimer, R. *see* Vuylsteke, A., (*EACTA*) A.30; (*EACTA*) A.51; (*EACTA*) A.77

Latimer, R. D. *see* Gota, M., (*EACTA*) A.20; Poulton, B. B., (*EACTA*) A.29

Laurence, A. S. *see* Sabar, M. A., (*ARS*) 584P

Laurent, S. *see* Baele, Ph., (*EACTA*) A.60

Lauwers, P. *see* Gouwy, S., (*EACTA*) A.59; Meyns, B., (*EACTA*) A.38

Lavoie, J., Vischoff, D. and Villeneuve, E. Comparison of caudally administered morphine *vs* hydromorphone in paediatric cardiac surgical patients, (*EACTA*) A.70

Lawes, E. G. Volume preloading, spinal anaesthesia and Caesarean section, (*C*) 334–335

Lawler, P. G. P. *see* Wood, P. R. 563–564

Lawson, G. M. *see* Southorn, P. 467–469

Lawson, R. A. *see* Wolf, A. R. 362–364

Laycock, S. K. *see* Van de Velde, M., (*EACTA*) A.3

Layher, Y. *see* Myles, P. S. 694–698

Leather, A. *see* Van de Velde, M., (*EACTA*) A.3

Lee, C., Zhang, X. and Kwan, W.-F. Electromyographic and mechanomyographic characteristics of neuromuscular block by magnesium sulphate in the pig 278–283

Lee, D. J. H., Robinson, D. L. and Soni, N. Efficiency of a circle system for short surgical cases: comparison of desflurane with isoflurane 780–782

Lee, J. S. and Abboud, T. Intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia, (*C*) 169–170

Lehot, J. J., Neidecker, J., Dalmas, J. P., Vedrinne, C., Flamens, C. and Bompard, D. Echocardiography by the anaesthetist: a French survey, (*EACTA*) A.43

Lehot, J. J. *see* Filley, S., (*EACTA*) A.63; Paulus, S., (*EACTA*) A.73; Vedrinne, C., (*EACTA*) A.66; (*EACTA*) A.85

Lenhart, F.-P. *see* Welte, M. 90–98

Lentschener, C. and Benhamou, D. Aprotinin during liver transplantation, (*C*) 882

Letzen, S. *see* Palm, S., (*ARS*) 588–589P

Leunens, V. *see* Van de Velde, M., (*EACTA*) A.3

Leuwer, M., Heine, J. F., Arseniev, L., Scheinichen, D., Jäger, K. and Piepenbrock, S. Flow cytometry evaluation of the *in vitro* effects of four i.v. anaesthetics on the respiratory burst of human neutrophils, (*ARS*) 585P

Levack, I. D., Bowie, R. A., Braid, D. P., Asbury, A. J., Marshall, R. L., Slawson, K. B., Birrell, H. and Gillon, K. R. W. Comparison of the effect of two dose schedules of oral omeprazole with oral ranitidine on gastric aspirate pH and volume in patients undergoing elective surgery 567–569

Levraut, J. *see* Raucoules-Aimé, M. 198–202

Levy, J. *see* Vuylsteke, A., (*EACTA*) A.30; (*EACTA*) A.77

Licker, M., Bednarkiewicz, M., Neidhart, P., Prêtre, R., Montessuit, M., Favre, H. and Morel, D. R. Preoperative inhibition of angiotensin-converting enzyme improves systemic and renal haemodynamic changes during aortic abdominal surgery 632–639

Licker, M. *see* Schweizer, A., (*EACTA*) A.55

Lillywhite, N. *see* Driver, I., (*c*) 175

Lim, G. *see* Robbins, P. M., (*C*) 170

Lim, T. A. *see* Short, T. G. 313–315

Lin, E. S. Airway pressure signals during high frequency jet ventilation, (*ARS*) 576–577P

Lindahl, M. *see* Håkanson, E., (*EACTA*) A.1

Lindblom, D. *see* van der Linden, J., (*EACTA*) A.82

van der Linden, J., Astudillo, R., Rådegran, K., Hansson, L.-O. and Åberg, B. Elevated serum levels of S-100 after deep hypothermic circulatory arrest correlate with duration of circulatory arrest, (*EACTA*) A.84

van der Linden, J., Bengtsson, L. and Lindblom, D. Epiaortic scanning of the ascending aorta identifies arteriosclerotic plaques and changes surgical practice during CABG? (*EACTA*) A.82

Lindeque, B. G. *see* Wilson, A. J. 515–518

Lindsay, S. L. *see* Cooper, D. W. 611–615

Linkens, D. A. *see* Mason, D. G. 396–400

Littlejohn, I. H. *see* Toner, C. C. 347–351

Llobel, F. and Laorden, M. L. Effects of morphine on atrial preparations obtained from non-failing and failing human hearts 106–110

Loken, R. G. *see* Maltby, J. R., (*C*) 333

López-Olaondo, L., Carrascosa, F., Pueyo, F. J., Monedero, P., Busto, N. and Sáez, A. Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting 835–840

Lötte, A. *see* Karzai, W. 5–8

Lugrin, D. *see* Isetta, C., (*EACTA*) A.52

Lundberg, C. *see* Dahlin, L. G., (*EACTA*) A.62

Lynch, C. *see* Vuylsteke, A., (*EACTA*) A.30; (*EACTA*) A.77

Lyons, B., Kirby, F. and Casey, W. Parental or anaesthetist's ability to predict a 'stormy' induction in young children, (*ARS*) 589P

Lyons, G. *see* Hawthorne, L. 680–684

McAteer, E. M. *see* Mellor, D. J. 621–623

McBeth, C. *see* Asai, T. 772–776

McClure, J. H. Ropivacaine 300–307

McCoy, E. P., Mirakhur, R. K., Maddineni, V. R., Wierda, J. M. K. H. and Proost, J. H. Pharmacokinetics of rocuronium after bolus and continuous infusion during halothane anaesthesia 29–33

McDonald, D. S. Venous thromboembolism and cardiovascular surgery, (*C*) 473

Macdonald, I. A. *see* Carli, F., (*E*) 601–603

MacDowell, C. *see* Buggy, D., (*C*) 887; Buggy, D. J. 319–321

McFarlane, H. *see* Kulkarni, V., (*ARS*) 586P

McGowan, C., Heaton, B. and Stephenson, R. N. Occupational x-ray exposure of anaesthetists 868–869

McGowan, P. Improving preoxygenation, (*C*) 748

McGreggor, R. *see* Shannon, C., (*C*) 472
McHardy, F. E. *see* Cooper, D. W. 611–615
McIndoe, A. K. and Hammond, E. J. Cardiac arrest at induction of anaesthesia for Caesarean section, (*C*) 332–333
Macintyre, P. E. and Ready, L. B. *Acute Pain Management: A Practical Guide, (R)* 892
McKenzie, A. G. and Mathe, S. Interpleural local anaesthesia: anatomical basis for mechanism of action 297–299
Mackersie, A. M. Change in neostigmine ampoules, (*C*) 334
McQuay, H. *see* Tramèr, M. 186–193; (*C*) 473–474
McQuillan, P. M. *see* Hahn, M. B., (*R*) 751
Madden, N. *see* Norman, B. 163–166
Maddineni, V. R. *see* McCoy, E. P. 29–33
Maekawa, N. *see* Mikawa, K. 221–226
Magboul, M. A. *see* Naguib, M., (*e*) 339
Maier, C. *see* Palm, S., (*ARS*) 588–589P
Makin, A. P. *see* Munro, F. J. 156–159; (*C*) 888–889
Malagon, I. Haemodynamic effects of air travel, (*ARS*) 590P
Mallick, A. and Moss, E. Venous air embolism: is end-tidal oxygen monitoring more informative than end-tidal carbon dioxide? (*C*) 475
Mallick, A., Samaan, A. and Braithwaite, P. Volume preloading, spinal anaesthesia and Caesarean section, (*C*) 335
Maloney, D. G. *see* Dòpfmer, U. R. 77–80
Maltby, J. R., Hamilton, R. C. and Loken, R. G. Day-case cataract surgery, (*C*) 333
Manhold, C. *see* Brase, R., (*EACTA*) A.47
Manners, J. M. Use of i.m. temperature probes during cardiopulmonary bypass in humans, (*C*) 471–472
Mansfield, M. D., James, K. S. and Kinsella, J. Influence of dose and timing of administration of morphine on postoperative pain and analgesic requirements 358–361
Mapleson, W. W. Effect of age on MAC in humans: a meta-analysis 179–185
Mapleson, W. W. *see* Evans, M. J., (*C*) 334; Johnston, K. R. 401–404; Wilkes, A. R. 737–739
Maran, N. J., Knill-Janes, R. P. and Spence, A. A. Infertility among female hospital doctors in the UK, (*ARS*) 581P
Marchandise, B. *see* Broka, S., (*EACTA*) A.44
Mares, P., Hiesmayr, M., Rajek, A., Laßnigg, A., Wislocki, W., Klepetko, W. and Haider, W. Minimal incidence of reperfusion pulmonary oedema after pulmonary thromboendarterectomy, (*EACTA*) A.75
Marino, G. *see* Oppizzi, M., (*EACTA*) A.46
Maritz, J. S. *see* Coetzee, J. F. 415–418
Marjot, R. *see* Morris, G. N. 456–458
Markey, G. *see* Royston, B., (*ARS*) 582–583P
Marota, J. J. A. *see* Goto, T. 702–706
Marsch, S. C. U. *see* Dalmas, S. 419–427
Marshall, R. L. *see* Levack, I. D. 567–569
Martin, D. E. *see* Hensley, F. A. jr, (*R*) 174
Martin, E. *see* Schmidt, H. 707–712
Martlew, R. A., Meakin, G., Wadsworth, R., Sharples, A. and Baker, R. D. Dose of propofol for laryngeal mask airway insertion in children: effect of premedication with midazolam 308–309
Marx, E. *see* Laßnigg, A., (*EACTA*) A.18
Masaki, H. *see* Denda, S. 258–265
Mason, D. G., Edwards, N. D., Linkens, D. A. and Reilly, C. S. Performance assessment of a fuzzy controller for atracurium-induced neuromuscular block 396–400
Mateo, J. *see* Langeron, O. 783–789
Mathe, S. *see* McKenzie, A. G. 297–299
Mather, S. J. *see* Hughes, D. G., (*R*) 599
Matson, A. *see* Richmond, C. E. 446–448
Matsuki, A. *see* Hirota, K. 266–270
Matta, B. F. and Stow, P. J. Sepsis-induced vasoparalysis does not involve the cerebral vasculature: indirect evidence from autoregulation and carbon dioxide reactivity studies 790–794
Mayné, A. *see* Broka, S., (*EACTA*) A.44
Mayor, A. H., Hughes, P., Ryder, I. and Sneyd, J. R. Magnetic resonance imaging of the superior vena cava during spontaneous respiration with continuous positive airway pressure via a facemask in normal subjects, (*ARS*) 578–579P
Mazoit, J.-X. *see* Nyarwaya, J.-B. 428–434
Mazzeo, A. J., Cheng, E. Y., Bosnjak, Z. J., Coon, R. L. and Kampine, J. P. Differential effects of desflurane and halothane on peripheral airway smooth muscle 841–846
Mead, M. *see* Stanley, G. 484–486
Meagher, J. *see* Ireland, N. 657–662
Meakin, G. *see* Martlew, R. A. 308–309
Mellinghoff, H. *see* Nigrovic, V., (*ARS*) 580–581P
Mellor, D. J., Moss, E., McAteer, E. M. and Shah, M. V. Effect of antagonism of mivacurium on recovery of extraocular muscle function 621–623
Meretoja, O. A., Taivainen, T., Räihä, L., Korpela, R. and Wirtavuori, K. Sevoflurane–nitrous oxide or halothane–nitrous oxide for paediatric bronchoscopy and gastroscopy 767–771
Meretoja, O. A., Wirtavuori, K., Taivainen, T. and Olkkola, K. T. Time course of potentiation of mivacurium by halothane and isoflurane in children 235–238
Merli, M. *see* Paino, R., (*EACTA*) A.40
Merville, C. *see* Isetta, C., (*EACTA*) A.52
Mets, B. *see* James, M. F. M. 713–720
Metzler, H. *see* Fruhwald, S., (*EACTA*) A.65
Meyns, B., Sergeant, P., Demeyere, R., Vandommele, J., Lauwers, P., Ferdinande, P., Verwaest, C., Daenen, W. and Flameng, W. The hemopump as left ventricular assist device in postcardiotomy heart failure, (*EACTA*) A.38
Mezzatesta, J. *see* Turner, G. 606–610
Mielck, F., Stephan, H., Scholz, M., Hoeft, A. and Sonntag, H. A new method for cerebral blood flow measurement, (*EACTA*) A.12
van Miert, M. M. *see* O'Keefe, V., (*ARS*) 585P
Mikawa, K., Nishina, K., Maekawa, N. and Obara, H. Comparison of nicardipine, diltiazem and verapamil for controlling the cardiovascular responses to tracheal intubation 221–226
Milazzo, F. *see* Paino, R., (*EACTA*) A.40
Millar, K. *see* Tzabar, Y. 194–197
Milligan, K. R. *see* Bunting, H. E., (*C*) 596
Mills, P. *see* Driver, I., (*e*) 175
Milroy, S. J. *see* Cottam, S., (*C*) 882
Mirakhur, R. K. *see* McCoy, E. P. 29–33
Mitsuhata, H. *see* Ikeno, S. 573–575
Mohadjer, A. *see* Walpoth, B. H., (*EACTA*) A.7
Møiniche, S. *see* Pedersen, J. L. 806–810
Molliex, S., Navez, M., Baylot, D., Prades, J. M., Elkhoury, Z. and Auboyer, C. Regional anaesthesia for outpatient nasal surgery 151–153
Moloney, J. T. *see* Myles, P. S. 694–698
Monedero, P. *see* López-Olaondo, L. 835–840
Montessuit, M. *see* Licker, M. 632–639
Montgomery, J. E., Kestin, I. G., Sneyd, J. R. and Sutherland, C. J. Morphine consumption in patients receiving rectal paracetamol and diclofenac alone and in combination, (*ARS*) 591–592P
Montorsi, E. *see* Oppizzi, M., (*EACTA*) A.81
Mooney, P. *see* Turner, G. 606–610
Mooney, P. H. *see* Schug, S. A. 487–491
Moore, A. *see* Tramèr, M. 186–193; (*C*) 473–474
Moratin, P. *see* Smith, T. 452–455
Morel, D. R. *see* Licker, M. 632–639
Mori, K. *see* Kurata, J. 721–725
Moritz, A. *see* Rajek, A., (*EACTA*) A.39
Morley, A. P. Prehospital monitoring of trauma patients: experience of a helicopter emergency medical service 726–730
Morris, G. N. and Marjot, R. Laryngeal mask airway performance: effect of cuff deflation during anaesthesia 456–458
Morrison, L. M. M. *see* Espinet, A. 209–213
Morton, N. S. Prevention of vomiting after paediatric strabismus surgery, (*C*) 473
Moshal, D. C. *see* Knowles, P. R., (*EACTA*) A.42
Moss, E. *see* Mallick, A., (*C*) 475; Mellor, D. J. 621–623
Mottram, S. D. *see* Raphael, J. H. 116–121
Mphanza, T. Inadvertent infusion of glucose saline into the extradural space, (*C*) 332
Mubagwa, K. *see* Herijgers, P., (*EACTA*) A.13
Munglani, R., Fleming, B. G. and Hunt, S. P. Remembrance of times past: the significance of c-*fos* in pain, (*E*) 1–4
Munro, F. J., Makin, A. P. and Reid, J. Airway problems after carotid endarterectomy 156–159; Cervical haematoma and airway obstruction, (*C*) 888–889
Murakawa, M. *see* Kurata, J. 721–725
Murday, V. *see* Price, C. M. 464–466
Murphy, P. G., Davies, M. J., Columb, M. O. and Stratford, N. Effect of propofol and thiopentone on free radical mediated oxidative stress of the erythrocyte 536–543
Murray, G. *see* Smith, E., (*EACTA*) A.86
Murray, J. M. *see* Gormley, W. P. 802–805
Mushambi, M. C., Halligan, A. W. and Williamson, K. Management of pre-eclampsia, (*C*) 889–890; Recent developments in the pathophysiology and management of pre-eclampsia 133–148
Mushambi, M. C. *see* Fox, A., (*C*) 336
Myles, P. S. Systolic pressure variation—a way to recognize dynamic hyperinflation, (*C*) 169
Myles, P. S., Hendrata, M., Layher, Y., Williams, N. J.,

Hall, J. L., Moloney, J. T. and Powell, J. Double-blind, randomized trial of cessation of smoking after audiotape suggestion during anaesthesia 694–698

Nadziakiewicz, P. *see* Knapik, P., (*EACTA*) A.28
Naguib, M. Histamine release by neuromuscular blocking agents, (*C*) 471
Naguib, M., Samarkandi, A. H., Bakhamees, H. S., Magboul, M. A. and El-Bakry, A. K. Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine, (*e*) 339
Nakao, S. *see* Kurata, J. 721–725
Nathanson, M. *see* Smith, I. 435–445
Nathorst-Westfelt, U. *see* Haraldsson, Å., (*EACTA*) A.27
Nathwani, D., Rich, P., Konieczko, K. M. and Ramachandra, V. Midazolam *vs* trimeprazine premedication for children during day-care surgery, (*ARS*) 589P
Nathwani, D. *see* Brunner, M. D. 34–37; Pal, S. K., (*ARS*) 577P
Navez, M. *see* Molliex, S. 151–153
Nay, P. G. Nebulized lignocaine before gaseous induction with desflurane, (*C*) 596
Neidecker, J. *see* Lehot, J. J., (*EACTA*) A.43; Vedrinne, C., (*EACTA*) A.66
Neidhart, P. *see* Licker, M. 632–639; Walpoth, B. H., (*EACTA*) A.7; (*EACTA*) A.58
Neskovic, V. *see* Sindjelic, R., (*EACTA*) A.19
Newman, S. P. *see* Arowsmith, J. E., (*EACTA*) A.83
Newton, D. E. F. *see* Brunner, M. D. 34–37; (*C*) 881; Crabb, I. 795–801; Pal, S. K., (*ARS*) 577P; Richmond, C. E. 446–448
Newton, M. C., Chadd, G. D., O'Donoghue, B., Sapsed-Byrne, S. M. and Hall, G. M. Metabolic and hormonal responses to induced hypotension for middle ear surgery 352–357
Niemi, T. T., Kuitunen, A. H., Vahtera, E. M. and Rosenberg, P. H. Haemostatic changes caused by i.v. regional anaesthesia with lignocaine 822–828
Nigrovic, V., Mellinghoff, H. and Buzello, W. Modelling the interaction of two neuromuscular blocking agents: generation of an additive or a supra-additive neuromuscular block, (*ARS*) 580–581P
Nigrovic, V. *see* Beaufort, A. M., (*ARS*) 580P
Ninet, J. *see* Vedrinne, C., (*EACTA*) A.66
Nishikawa, T. Extradural clonidine for postoperative pain relief, (*C*) 171; Extradural clonidine for postoperative pain relief, (*C*) 881–882
Nishimura, Y. *see* Herijgers, P., (*EACTA*) A.14
Nishina, K. *see* Mikawa, K. 221–226
Nordlander, M., Björkman, J.-A., Regårdh, C-G. and Thalén, P. Pharmacokinetics and haemodynamic effects of an ultrashort-acting calcium antagonist, (*EACTA*) A.24
Nordström, O. and Sandin, R. Recall during intermittent propofol anaesthesia 699–701
Norman, B., Soni, N. and Madden, N. Anaesthesia and juvenile hyaline fibromatosis 163–166
Norman, M. *see* Gelinder, S., (*EACTA*) A.80
Nyarwaya, J.-B., Pierre, S., Mazoit, J.-X., Umbrain, V., Romain, M., Samii, K. and d'Hollander, A. Effects of carbon dioxide embolism with nitrous oxide in the inspired gas in piglets 428–434
Nylander, E. *see* Dahlin, L. G., (*EACTA*) A.62
Nylund, U. *see* Reber, A. 760–766
Nyström, P. *see* Vuylsteke, A., (*EACTA*) A.51

Obara, H. *see* Mikawa, K. 221–226
O'Beirne, H. and Bellamy, M. C. Effects of desflurane and isoflurane on splanchnic microcirculation during surgery, (*ARS*) 592P
O'Beirne, H. *see* Bellamy, M. C., (*ARS*) 587P
O'Beirne, H. A. *see* Snook, N. J. 740–743
O'Callaghan, C. *see* Raphael, J. H. 116–121
O'Donoghue, B. *see* Newton, M. C. 352–357
Oduro, A. *see* Vuylsteke, A., (*EACTA*) A.51
Oduro-Dominah, A. *see* Dhond, G., (*EACTA*) A.57
Oh, T. E. Gastric tonometry to monitor tissue oxygenation: more than a gut feeling? (*E*) 604–605
O'Keefe, V., van Miert, M. M., Parker, C. J. R., Salmon, P. and Shenkin, A. Patient-controlled analgesia and the plasma glucose response to surgery, (*ARS*) 585P
O'Leary, E., Hubbard, K., Tormey, W. and Cunningham, A. J. Laparoscopic cholecystectomy: haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position 640–644
Olin, C. *see* Svedjeholm, P., (*EACTA*) A.61
Olkkola, K. T. *see* Meretoja, O. A. 235–238
Olofsen, E. *see* Boer, F. 203–208
Olsson, J. and Hahn, R. G. Analysis of ethanol in expired air during low-flow isoflurane anaesthesia 85–89
Oppizzi, M., Montorsi, E., Guarracino, F., Vendrame, G., Gerli, C. and Paolillo, G. The efficacy of enoximone in improving the postoperative course of cardiac patients with severe myocardial dysfunction, (*EACTA*) A.81
Oppizzi, M., Zoia, E., Guarracino, F., Marino, G., Vendrame, G., Franco, A. and Paolillo, G. Postoperative diastolic dysfunction. Incidence, natural history and prognosis, (*EACTA*) A.46
Oppizzi, M. *see* Guarracino, F., (*EACTA*) A.45
Oppizzi, O. *see* Casati, V., (*EACTA*) A.53
Orlando, A. *see* Curatolo, M., (*e*) 598
Orre, L. *see* Gelinder, S., (*EACTA*) A.80
Otten, Ph. *see* Wilder-Smith, O. H. G. 816–821
Owen-Reece, H., Elwell, C. E., Harkness, W., Goldstone, J., Delpy, D. T., Wyatt, J. S. and Smith, M. Use of near infrared spectroscopy to estimate cerebral blood flow in conscious and anaesthetized adult subjects 43–48
Özdener, F. *see* Süzer, Ö, (*EACTA*) A.68
Özkan, A. K. *see* Süzer, Ö, (*EACTA*) A.68
Özkul, V. *see* Özyurt, A., (*EACTA*) A.25
Özler, A. *see* Özyurt, A., (*EACTA*) A.25; Toraman, F., (*EACTA*) A.21
Özüner, Z. *see* Süzer, Ö, (*EACTA*) A.68
Özyurt, A., Özkul, V., Aksoy, N., Yapýcý, F., Yurtseven, N., Erdemir, H., Ünal, Ö., Daðsalý, S., Özler, A., Canik, S. and Kopman, E. Hypotension following the administration of fentanyl-diazepam combination in chronic ACE inhibitor users, (*EACTA*) A.25

Paino, R., Milazzo, F., Amari, B., Visigalli, M., Ferrante, M. and Merli, M. Continuous temperature and O_2 saturation monitoring of jugular blood during DHCA procedures for aortic surgery, (*EACTA*) A.40
Pal, S. K., Sharpe, R., Nathwani, D. and Newton, D. E. F. Auditory evoked responses, median frequency and 95% spectral edge during anaesthesia with desflurane and nitrous oxide, (*ARS*) 577P
Pal, S. K., Zych, Z., Rajendram, R. and White, D. C. Economy during induction of anaesthesia: a comparison of desflurane with isoflurane via a circle system, (*ARS*) 582P
Palazzo, M. G. A. *see* Toner, C. C. 347–351
Palm, S., Letzen, S., Steinmann, J. and Maier, C. Immunoglobulin and interleukin 2 production *ex vivo/in vitro* during treatment with oral retarded morphine, (*ARS*) 588–589P
Palmer, M. *see* Heath, K. J. 877–878
Panic, G. *see* Jovic, M., (*EACTA*) A.49
Pansard, J.-L. *see* Langeron, O. 783–789
Paolillo, G. *see* Casati, V., (*EACTA*) A.53; Guarracino, F., (*EACTA*) A.45; Oppizzi, M., (*EACTA*) A.46; (*EACTA*) A.81
Park, G. R. and Kang, Y., (editors) *Anesthesia and Intensive Care for Patients with Liver Disease*, (*R*) 338
Park, G. R. and Sladen, R. N., (editors) *Sedation and Analgesia in the Critically Ill*, (*R*) 174
Parker, C. J. R. *see* Boyd, A. H. 382–388; O'Keefe, V., (*ARS*) 585P
Parkins, J. *see* Tremlett, M. R., (*ARS*) 583–584P
Parkinson, R. *see* Joyce, C. J. 292–296
Parmar, M. and Scott, R. P. F. Mivacurium chloride and late onset congenital myopathy 160–162
Parry, M. G. *see* Fernando, R., (*C*) 886–887
Pasch, T. *see* Weiss, B. M. 405–411
Paulus, S., Bastien, O., Flamens, C., Deplace, C. and Lehot, J. J. Non-invasive pressure support ventilation (NPSV) as an alternative to reintubation, (*EACTA*) A.73
Pavlovic, G. *see* Sindjelic, R., (*EACTA*) A.19
Payne, J. *see* Schug, S. A. 487–491
Pearson, A. J., Pomfrett, C. J. D., Doran, B. R. H. and Pollard, B. J. Evaluation of bispectral index as an objective sedation score in the intensive care unit, (*ARS*) 577–578P
Péastaing, M. *see* Calvert, B., (*EACTA*) A.78
Pedersen, J. L., Callesen, T., Møiniche, S. and Kehlet, H. Analgesic and anti-inflammatory effects of lignocaine–prilocaine (EMLA) cream in human burn injury 806–810
Pehkonen, E. J. *see* Honkonen, E. L., (*EACTA*) A.6
Perel, A. and Segal, E. Systolic pressure variation—a way to recognize dynamic hyperinflation, (*C*) 168–169
Peshin, P. K. *see* Poulton, B. B., (*EACTA*) A.29
Peter, K. *see* Welte, M. 90–98

Petersen, K. L. *see* Ilkjaer, S. 829–834

Petersen-Felix, S. *see* Curatolo, M. 245–250; Roth, D. 38–42

Pétrie, J., Bourel, P., Saint-Maurice, O. and Folliguet, T. Very low dose aprotinin in cardiac surgery, (*EACTA*) A.54

Petrovic, P. *see* Sindjelic, R., (*EACTA*) A.19

Pfaffendorf, M. *see* Vroom, M. B. 122–129

Philbin, D. M. *see* Dalmas, S. 419–427

Philipp, A. *see* Rödig, G. 9–12

Phillips, S., Daborn, A. K. and Hatch, D. J. Preoperative fasting for paediatric anaesthesia, (*C*) 471

Pichler, B. *see* Welte, M. 90–98

Piepenbrock, S. *see* Leuwer, M., (*ARS*) 585P

Pierce, J. M. T. *see* Deakin, C. D., (*EACTA*) A.41

Pierre, S. *see* Nyarwaya, J.-B. 428–434

Pietersen, H. G., Langenberg, C. J. M., Geskes, G., Wagenmakers, A. J. M., de Lange, S. and Soeters, P. B. Free fatty acid (FFA) uptake immediately after routine coronary artery bypass surgery (CABG), (*EACTA*) A.2

Pilkington, S. *see* Hett, D., (*EACTA*) A.33

Pintanel, T. *see* Rodríguez-Chinchilla, R. 328–329

Pittard, A. J., Banks, R. E., Galley, H. F. and Webster, N. R. Soluble E-cadherin concentrations in patients with systemic inflammatory response syndrome and multiorgan dysfunction syndrome 629–631

Pittard, A. J., Webster, N. R. and Bellamy, M. C. Predictability of tumour necrosis factor concentration: evidence for a mechanism for mutual regulation of autacoids in systemic inflammatory response syndrome, (*ARS*) 587P

Podesser, B. *see* Rajek, A., (*EACTA*) A.39

Polhill, S. L. and Smith, D. C. Evoked EMG response during inhalation of a subanaesthetic concentration of isoflurane, (*ARS*) 578P

Pollard, B. J. *see* Bryan, A., (*ARS*) 579P; Pearson, A. J., (*ARS*) 577–578P

Pomfrett, C. J. D. *see* Healy, T. E. J., (*C*) 885–886; Pearson, A. J., (*ARS*) 577–578P

Ponte, J. Suxamethonium and auditory evoked potentials, (*C*) 881

Ponte, J. *see* Harrison, S. J. 511–514

Popat, M. T. *see* Carrie, L. E. S., (*R*) 892–893

Popivic, A. *see* Jovic, M., (*EACTA*) A.49

Popovic, Z. *see* Jovic, M., (*EACTA*) A.49

Porsius, M. *see* van der Stroom, J. G. 645–651

Porter, S. S., (editor) *Anaesthesia for Surgery of the Spine*, (*R*) 892

Poulton, B. B., Baddoo, H. H. K., Doyle, A. R., Stevens, J. J. W. M., Kirkham, A. J. T. and Duthie, D. J. R. Remifentanil by infusion achieves predictable blood concentrations, (*EACTA*) A.15

Poulton, B. B., Hall, L. W., Latimer, R. D. and Peshin, P. K. Nitric oxide and pulmonary impedance, (*EACTA*) A.29

Powell, J. *see* Myles, P. S. 694–698

Powney, J. G. *see* Toner, C. C. 347–351

Pozzi, M. *see* Karmakar, M. K. 811–815

Prades, J. M. *see* Molliex, S. 151–153

Pratschke, E. *see* Welte, M. 90–98

Preciado, M. J. *see* Aguilar, J. L. 72–76

Prêtre, R. *see* Licker, M. 632–639; Schweizer, A., (*EACTA*) A.55

Price, C. M., Ford, S., St John Jones, L. and Murday, V. Myocardial ischaemia associated with Ehlers–Danlos syndrome 464–466

Price, W. *see* Cochran, D. 570–572

Priebe, H.-J. *see* Karzai, W. 5–8

Prinzen, F. W. *see* Wetherings, C. J., (*EACTA*) A.8; Willigers, H. M. M., (*EACTA*) A.23

Proost, J. H. *see* Beaufort, A. M., (*ARS*) 580P; McCoy, E. P. 29–33

Pueyo, F. J. *see* López-Olaondo, L. 835–840

Pugsley, W. B. *see* Arowsmith, J. E., (*EACTA*) A.83

Rabito, S. F. *see* Hirota, K. 266–270

Rådegran, K. *see* van der Linden, J., (*EACTA*) A.84

Radomir, B. *see* Jovic, M., (*EACTA*) A.49

Rafferty, T. D., (editor) *Basics of Transoesophageal Echocardiography*, (*R*) 173

Rahmig, H. *see* Weiss, B. M. 405–411

Räihä, L. *see* Meretoja, O. A. 767–771

Rajek, A., Podesser, B., Kupilik, N., Hiesmayr, M., Moritz, A. and Haider, W. Effect of β-blockers *versus* calcium channel blockers in myocardial revascularization without cardiopulmonary bypass in pigs, (*EACTA*) A.39

Rajek, A. *see* Mares, P., (*EACTA*) A.75

Rajendram, R. *see* Pal, S. K., (*ARS*) 582P

Ramachandra, V. *see* Nathwani, D., (*ARS*) 589P

Randall, N. *see* Davis, G. 879–880

Randell, T. *see* Kyttä, J., (*C*) 475–476

Randour, P. *see* Broka, S., (*EACTA*) A.44

Ranucci, M., Conti, D., Cirri, S., Conti, E. and Soro, G. Heparin-coated circuits reduce postoperative lung complications in high-risk cardiac patients, (*EACTA*) A.71

Raphael, J. H., Selwyn, D. A., Mottram, S. D., Langton, J. A. and O'Callaghan, C. Effects of 3 MAC of halothane, enflurane and isoflurane on cilia beat frequency of human nasal epithelium *in vitro* 116–121

Raphael, J. H., Strupish, J., Selwyn, D. A., Hann, H. C. L. and Langton, J. A. Recovery of respiratory ciliary function after depression by inhalation anaesthetic agents: an *in vitro* study using nasal turbinate explants 854–859

Raphael, J. H. *see* Hann, H. C. L., (*ARS*) 591P; Selwyn, D. A. 111–115; 274–277

Räsänen, J. *see* Karinen, J. 616–620

Ratcliffe, R. M. H. *see* Döpfmer, U. R. 77–80

Raucoules-Aimé, M., Labib, Y., Levraut, J., Gastaud, P., Dolisi, C. and Grimaud, D. Use of i.v. insulin in well-controlled non-insulin-dependent diabetics undergoing major surgery 198–202

Rauscher, J. *see* Lampert, R., (*EACTA*) A.11

Rautoma, P. *see* Teiriä, H. 154–155

Ready, L. B. *see* MacIntyre, P. E., (*R*) 892

Reber, A., Engberg, G., Sporre, B., Kviele, L., Rothen, H.-U., Wegenius, G., Nylund, U. and Hedenstierna, G. Volumetric analysis of aeration in the lungs during general anaesthesia 760–766

Reber, A., Huber, P. R., Ummenhofer, W., Gürtler, C., Zurschmiede, C., Khan, Z. and Schneider, M. Changes in pineal and pituitary hormone secretion under general anaesthesia, (*ARS*) 584P

Redfern, N. *see* Thomas, D. G. 61–65; Tremlett, M. R., (*ARS*) 583–584P

Reeve, W. *see* Smith, E., (*EACTA*) A.86

Regårdh, C-G. *see* Nordlander, M., (*EACTA*) A.24

Reid, J. and Thorburn, J. Volume preloading, spinal anaesthesia and Caesarean section, (*C*) 335–336

Reid, J. *see* Munro, F. J. 156–159; (*C*) 888–889

Reilly, C. S. *see* Mason, D. G. 396–400

Reneman, R. S. *see* Wetherings, C. J., (*EACTA*) A.8

Reynolds, F. Maternal sequelae of childbirth, (*C*) 474–475

Reynolds, F. *see* Eddleston, J. M. 66–71

Ricco, J. B. *see* Karayan, J. 459–460

Rich, P. *see* Nathwani, D., (*ARS*) 589P

Rich, P. A. *see* Brunner, M. D. 34–37

Richards, K., England, A. J. and Feldman, A. Effect of stimulation rate on force of contraction in partially paralysed rat phrenic nerve hemidiaphragm preparations, (*ARS*) 579–580P

Richards, K. *see* England, A. J., (*ARS*) 592–593P

Richmond, C. E., Matson, A., Thornton, C., Doré, C. J. and Newton, D. E. F. Effect of neuromuscular block on depth of anaesthesia as measured by the auditory evoked response 446–448

Ricksten, S-E. *see* Ederberg, S., (*EACTA*) A.17

Ricksten, S.-E. *see* Haraldsson, A., (*EACTA*) A.27; Vuylsteke, A., (*EACTA*) A.30; (*EACTA*) A.77

Rincón, R. *see* Aguilar, J. L. 72–76

Riou, B. *see* Langeron, O. 783–789

Ritter, L. *see* Capouet, V. 54–60

Robbins, P. M., Fernando, R. and Lim, G. Intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia, (*C*) 170

Roberts, D. H. *see* Davis, G. 879–880

Robertson, E. N. *see* Vanlinthout, L. E. H. 389–395

Robinson, B. J. *see* Galletly, D. C. 503–507

Robinson, D. L. *see* Lee, D. J. H. 780–782

Robson, S. C. *see* Thomas, D. G. 61–65

Rodichock, L. D. *see* Russell, G. B., (*R*) 477

Ródig, G., Keyl, C., Wiesner, G., Philipp, A. and Hobbhahn, J. Effects of sevoflurane and isoflurane on systemic vascular resistance: use of cardiopulmonary bypass as a study model 9–12

Rodríguez-Chinchilla, R., Rodríguez-Pont, A., Pintanel, T. and Vidal-López, F. Bilateral severe pain at L3–4 after spinal anaesthesia with hyperbaric 5% lignocaine 328–329

Rodríguez-Pont, A. *see* Rodríguez-Chinchilla, R. 328–329

Roe, P. G. *see* Farmery, A. D. 284–291; (*e*) 890

Rohling, R. *see* Weiss, B. M. 405–411

Rolly, G. *see* Versichelen, L. 668–672

Romain, M. *see* Nyarwaya, J.-B. 428–434

Rosenberg, J. *see* Rosenberg-Adamsen, S. 552–559

Rosenberg, P. *see* Hammarén, E., (*EACTA*) A.16

Rosenberg, P. H. *see* Niemi, T. T. 822–828

Rosenberg-Adamsen, S., Kehlet, H., Dodds, C. and Rosenberg, J. Postoperative sleep disturbances: mechanisms and clinical implications 552–559
Roth, D., Petersen-Felix, S., Bak, P., Arendt-Nielsen, L., Fischer, M., Bjerring, P. and Zbinden, A. M. Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by evoked potentials 38–42
Roth, E. *see* Hiesmayr, M., (*EACTA*) A.32; Laßnigg, A., (*EACTA*) A.18
Rothen, H.-U. *see* Reber, A. 760–766
Rowbotham, D. J. *see* Stanley, G. 484–486; Thompson, J. P., (*E*) 341–343
Royal College of Physicians of Edinburgh Consensus statement on autologous transfusion 470
Royston, B., Markey, G. and White, D. Performance of vaporizers in circle systems (II), (*ARS*) 582–583P
Rudlof, B. *see* Lampert, R., (*EACTA*) A.11
Russell, G. B. and Rodichock, L. D., (editors) *Primer of Intraoperative Neurophysiologic Monitoring*, (*R*) 477
Russell, I. F. and Wang, M. Isolated forearm technique, (*C*) 884–885
Rutberg, H. *see* Dahlin, L. G., (*EACTA*) A.62
Ruttmann, T. G., James, M. F. M. and Viljoen, J. F. Haemodilution induces a hypercoagulable state 412–414
Ryall, D. M. *see* Cooper, D. W. 611–615
Ryan Cook, D. *see* De Wolf, A. M. 624–628
Ryckwaert, F., Colson, P., Brunat, G. and Wintrebert, P. Standard pump flow rate and Sv_{O_2} above 60% do not imply adequate oxygen delivery during CPB, (*EACTA*) A.34
Ryder, I. *see* Mayor, A. H., (*ARS*) 578–579P
Ryder, W. A. *see* Dalmas, S. 419–427

Saba, G. *see* Booker, P. D. 365–368
Sabar, M. A., Gosling, A. J. and Laurence, A. S. Is tramadol better than ketorolac after day-case laparoscopy? (*ARS*) 584P
Sáez, A. *see* López-Olaondo, L. 835–840
St John Jones, L. *see* Price, C. M. 464–466
Saint-Maurice, O. *see* Pétrie, J., (*EACTA*) A.54
Saito, K. *see* Ikeno, S. 573–575
Saito, Y., Sakura, S. and Kosaka, Y. Ventilatory response to carbon dioxide, (*C*) 747–748
Saitoh, K. *see* Hirabayashi, Y., (*C*) 167; 508–510; (*C*) 886
Sakura, S. *see* Saito, Y., (*C*) 747–748
Salmon, P. *see* O'Keefe, V., (*ARS*) 585P
Samaan, A. *see* Mallick, A., (*C*) 335
Samarkandi, A. H. *see* Naguib, M., (*e*) 339
Samii, K. *see* Nyarwaya, J.-B. 428–434
Samra, G. S. *see* Toner, C. C. 347–351
Samuelson, S. *see* Gelinder, S., (*EACTA*) A.80
Sanchez, B. *see* Isetta, C., (*EACTA*) A.52
Sandin, R. *see* Nordström, O. 699–701
Sandor, V. *see* Gota, M., (*EACTA*) A.20
Sapsed-Byrne, S. M. *see* Newton, M. C. 352–357
Sariola-Heinonen, K. *see* Kentala, E., (*EACTA*) A.64
Sato, T. *see* Hirota, K. 266–270
Sattin, R. S. *see* Heriot, J. A. 325–327
Scaramozzino, P. *see* Curatolo, M., (*e*) 598
Scheinichen, D. *see* Leuwer, M., (*ARS*) 585P
Scheinin, H. *see* Kentala, E., (*EACTA*) A.64; Wilson, A. J. 515–518
Schlack, W., Hollmann, M., Stunneck, J. and Thämer, V. Effect of halothane on myocardial reoxygenation injury in the isolated rat heart 860–867
Schmid, E. R. *see* Schmidlin, D., (*EACTA*) A.48
Schmidlin, D., Jenni, R. and Schmid, E. R. Changes of mitral inflow patterns as assessed by transoesophageal echocardiography following cardiac surgery: are they of clinical significance? (*EACTA*) A.48
Schmidt, H., Secchi, A., Wellmann, R., Böhrer, H., Bach, A. and Martin, E. Effect of low-dose dopamine on intestinal villus microcirculation during normotensive endotoxaemia in rats 707–712
Schneider, M. *see* Reber, A., (*ARS*) 584P
Scholz, M. *see* Mielck, F., (*EACTA*) A.12
Schorn, B. *see* Buhre, W., (*EACTA*) A.37
Schug, S. A., Scott, D. A., Payne, J., Mooney, P. H. and Hägglöf, B. Postoperative analgesia by continuous extradural infusion of ropivacaine after upper abdominal surgery 487–491
Schweizer, A., Kalangos, A., Hohn, L., Jornod, N., Prêtre, R. and Licker, M. Aprotinin treatment does not impair renal function during and after cardiac surgery, (*EACTA*) A.55
Scott, C. A. *see* Smith, M. 499–502
Scott, D. *see* Turner, G. 606–610
Scott, D. A. *see* Schug, S. A. 487–491
Scott, R. P. F. *see* Parmar, M. 160–162
Scott, V. L. *see* De Wolf, A. M. 624–628
Sear, J. W. *see* Young, J. D. 652–656
Secchi, A. *see* Schmidt, H. 707–712
Secker, C., Hanning, C. D., Goodyer, P., Fothergill, J. and Jones, N. B. A novel fibreoptic pressure transducer system for the upper airway, (*ARS*) 581–582P
Segal, E. *see* Perel, A., (*C*) 168–169
Selldén, E., Bränström, R. and Brundin, T. Preoperative infusion of amino acids prevents postoperative hypothermia 227–234
Sellevold, O. F. M. *see* Kirkeby-Garstad, I., (*EACTA*) A.74
Selwyn, D. A., Gyi, A., Raphael, J. H., Key, A. and Langton, J. A. A perfusion system for *in vitro* measurement of human cilia beat frequency 111–115
Selwyn, D. A., Raphael, J. H., Lambert, D. G. and Langton, J. A. Effects of morphine on human nasal cilia beat frequency *in vitro* 274–277
Selwyn, D. A. *see* Raphael, J. H. 116–121; 854–859
Semple, D., Aldridge, L. A. and Doyle, E. Comparison of i.v. and s.c. diamorphine infusions for the treatment of acute pain in children 310–312
Senly, C. *see* Wilder-Smith, O. H. G. 816–821
Sergeant, P. *see* Herijgers, P., (*EACTA*) A.79; Meyns, B., (*EACTA*) A.38
Sett, P. K. *see* Watt, J. W. H. 870–871
Settergren, G. *see* Gårdebäck, M., (*EACTA*) A.36; Gelinder, S., (*EACTA*) A.80; Vuylsteke, A., (*EACTA*) A.30; (*EACTA*) A.77
Sewell, A. C. *see* Deakin, C. D., (*EACTA*) A.41
Shah, M. V. *see* Mellor, D. J. 621–623; Van Oldenbeek, C., (*EACTA*) A.22
Shah, T. *see* Arowsmith, J. E., (*EACTA*) A.83
Shannon, C., McGreggor, R. and Brunner, M. D. EEG arousal during laryngoscopy and intubation, (*C*) 472
Sharpe, R. *see* Pal, S. K., (*ARS*) 577P
Sharples, A. *see* Martlew, R. A. 308–309
Shenkin, A. *see* O'Keefe, V., (*ARS*) 585P
Sheplock, G. J. *see* Hahn, M. B., (*R*) 751
Sheppard, S. *see* Hett, D., (*EACTA*) A.33
Shibata, M. *see* Kurata, J. 721–725
Shichino, T. *see* Kurata, J. 721–725
Shieh, J. Y. *see* Sun, W. Z. 99–105
Shimizu, R. *see* Hirabayashi, Y., (*C*) 167; 508–510; (*C*) 886; Ikeno, S. 573–575
Shimoji, K. *see* Denda, S. 258–265
Short, T. G., Lim, T. A. and Tam, Y. H. Prospective evaluation of pharmacokinetic model-controlled infusion of propofol in adult patients 313–315
Shyu, B. C. *see* Sun, W. Z. 99–105
Sides, C. A. Pulsed saline lavage causing venous air embolism in a patient with Paget's disease 330–331
Simpson, P. J. *see* Carrie, L. E. S., (*R*) 892–893
Sindjelic, R., Vlajkovic, G., Vukotic, A., Neskovic, V., Stanic, M., Pavlovic, G. and Petrovic, P. Effect of anaesthetic agents on pulmonary shunt during coronary artery surgery, (*EACTA*) A.19
Sladen, R. N. *see* Park, G. R., (*R*) 174
Slawson, K. B. *see* Levack, I. D. 567–569
Sleigh, J. W. *see* Ireland, N. 657–662
Smart, D. *see* Wandless, A. L. 461–463
Smith, A. F. Improving preoxygenation, (*C*) 748
Smith, A. F., Thorpe, S. J. and Cook, L. B. Patient-controlled propofol: randomized, double-blind dose refinement, (*ARS*) 577P
Smith, D. *see* Conti, J., (*EACTA*) A.72; Hett, D., (*EACTA*) A.33
Smith, D. A. *see* De Wolf, A. M. 624–628
Smith, D. C. *see* Polhill, S. L., (*ARS*) 578P
Smith, E., Reeve, W., Murray, G., Woolman, P. and Colquhoun, A. Scoring systems *versus* subjective assessment as an outcome predictor in adult cardiac surgery, (*EACTA*) A.86
Smith, G. Impact factors in anaesthesia journals, (*E*) 753–754; The 11th World Congress of Anaesthesiology, (*E*) 479–480
Smith, G. B., Hamilton, R. C. and Carr , C. A. *Ophthalmic Anaesthesia—A Practical Handbook*, 2nd Edn, (*R*) 891
Smith, I., Nathanson, M. and White, P. F. Sevoflurane—a long-awaited volatile anaesthetic 435–445
Smith, M., Smith, S. J., Scott, C. A. and Harkness, W. F. J. Activation of the electrocorticogram by propofol during surgery for epilepsy 499–502
Smith, M. *see* Owen-Reece, H. 43–48
Smith, S. J. *see* Smith, M. 499–502
Smith, T., Moratin, P. and Wulf, H. Smaller children have greater bupivacaine plasma concentrations after ilioinguinal block 452–455

Sneyd, J. R. *see* Daniell, C. J., (*ARS*) 586–587P; Mayor, A. H., (*ARS*) 578–579P; Montgomery, J. E., (*ARS*) 591–592P
Snook, N. J., O'Beirne, H. A., Enright, S., Young, Y. and Bellamy, M. C. Use of recombinant human erythropoietin to facilitate liver transplantation in a Jehovah's Witness 740–743
Soeters, P. B. *see* Pietersen, H. G., (*EACTA*) A.2
Solombin, J. S. *see* Tellado, J. M., (*R*) 173–174
Soni, B. M. *see* Watt, J. W. H. 870–871
Soni, N. *see* Lee, D. J. H. 780–782; Norman, B. 163–166
Sonntag, H. *see* Buhre, W., (*EACTA*) A.37; Kazmaier, S., (*EACTA*) A.5; Mielck, F., (*EACTA*) A.12; Weyland, A., (*EACTA*) A.35
Soro, G. *see* Ranucci, M., (*EACTA*) A.71
Souter, A. *see* Stoneham, M., (*C*) 476
Souter, A. J. and Glynn, C. J. Ulnar and common peroneal nerve block revisited, (*C*) 595–596
Souter, M. J. and Andrews, P. J. D. Validation of the Edslab dual lumen oximetry catheter for continuous monitoring of jugular bulb oxygen saturation after severe head injury 744–746
Southorn, P., Vasdev, G. M. S., Chantigian, R. C. and Lawson, G. M. Reducing the potential morbidity of an unintentional spinal anaesthetic by aspirating cerebrospinal fluid 467–469
Spaeth, P. *see* Walpoth, B. H., (*EACTA*) A.58
Spahn, D. R. *see* Weiss, B. M. 405–411
Spence, A. A. *see* Maran, N. J., (*ARS*) 581P
Spens, H. J., Drummond, G. B. and Wraith, P. K. Changes in chest wall compartment volumes on induction of anaesthesia with eltanolone, propofol and thiopentone 369–373
Spittal, M. J. *see* Findlay, G. P. 526–529
Spittler, A. *see* Hiesmayr, M., (*EACTA*) A.32; Laßnigg, A., (*EACTA*) A.18
van der Spoel, H. I. *see* Jansen, P. G. M. 13–19
Sporre, B. *see* Reber, A. 760–766
Stacey, S. *see* Al-Shaikh, B., (*R*) 751
Stanic, M. *see* Sindjelic, R., (*EACTA*) A.19
Stanley, G., Appadu, B., Mead, M. and Rowbotham, D. J. Dose requirements, efficacy and side effects of morphine and pethidine delivered by patient-controlled analgesia after gynaecological surgery 484–486
Steinmann, J. *see* Palm, S., (*ARS*) 588–589P
Stephan, H. *see* Kazmaier, S., (*EACTA*) A.5; Mielck, F., (*EACTA*) A.12; Weyland, A., (*EACTA*) A.35
Stephenson, R. N. *see* McGowan, C. 868–869
Steven, C. M. *see* Heriot, J. A. 325–327
Stevens, J. J. W. M. *see* Poulton, B. B., (*EACTA*) A.15
Stickel, R. *see* Brase, R., (*EACTA*) A.47
Stoneham, M. and Souter, A. Spinal anaesthesia for Caesarean section in women with incomplete extradural analgesia, (*C*) 476
Stordeur, S. *see* Baele, Ph., (*EACTA*) A.60
Stow, P. J. *see* Matta, B. F. 790–794
Stratford, N. Effects of propofol on rabbit mesenteric arteries and veins, (*C*) 333
Stratford, N. *see* Murphy, P. G. 536–543
van der Stroom, J. G., van Wezel, H. B., Vergroesen, I., Kal, J. E., Koolen, J. J., Dijkhuis, J. P., Swaan, A., Porsius, M., Kleinjans, H. A. J. and van Zwieten, P. A. Comparison of the effects of urapidil and sodium nitroprusside on haemodynamic state, myocardial metabolism and function in patients during coronary artery surgery 645–651
Strunin, L. *see* Bullingham, A., (*C*) 473; Toner, C. C. 347–351
Strupish, J. *see* Raphael, J. H. 854–859
Stunneck, J. *see* Schlack, W. 860–867
Sturk, A. *see* Jansen, P. G. M. 13–19
Stygall, J. *see* Arowsmith, J. E., (*EACTA*) A.83
Sultana, A. *see* Turner, G. 606–610
Sun, W. Z., Shyu, B. C. and Shieh, J. Y. Nitrous oxide or halothane, or both, fail to suppress *c-fos* expression in rat spinal cord dorsal horn neurones after subcutaneous formalin 99–105
Sutherland, C. J. *see* Montgomery, J. E., (*ARS*) 591–592P
Sutherland, R. W. and Drummond, G. B. Effects of surgical skin incision on respiration in patients anaesthetized with enflurane 777–779
Süzer, A. *see* Süzer, Ö., (*EACTA*) A.9; Süzer, Ö, (*EACTA*) A.68
Süzer, Ö., Bozkurt, K., Süzer, A., Aykaç, Z. and Barlas, A. Levosimendan is a more potent inotropic agent than amrinone after ischaemia in isolated perfused guinea pig hearts, (*EACTA*) A.9
Süzer, Ö, Özkan, A. K., Özdener, F., Süzer, A., Aykaç, Z. and Özüner, Z. Trimetazidine does not reduce ischaemia-reperfusion induced arrhythmias in isolated perfused rat hearts, (*EACTA*) A.68
Svedjeholm, P., Dahlin, L. G. and Olin, C. Perioperative myocardial infarction (PMI) in cardiac surgery—risk factors and clinical outcome, (*EACTA*) A.61
Svedjeholm, R. *see* Dahlin, L. G., (*EACTA*) A.62; Håkanson, E., (*EACTA*) A.1
Svensson, S.-E. *see* Ederberg, S., (*EACTA*) A.17
Swaan, A. *see* van der Stroom, J. G. 645–651
Sykes, K. *Principles and Practice Series: Respiratory Support*, (*R*) 338
Szabo, Z. *see* Håkanson, E., (*EACTA*) A.1
Szécsi, J. *see* Herijgers, P., (*EACTA*) A.79

Tagesson, C. *see* Håkanson, E., (*EACTA*) A.1
Taivainen, T. *see* Meretoja, O. A. 235–238; 767–771
Tam, Y. H. *see* Short, T. G. 313–315
Tanskanen, P. *see* Kyttä, J., (*C*) 475–476
Tassonyi, E. *see* Fuchs-Buder, T. 565–566; Wilder-Smith, O. H. G., (*C*) 472–473; 816–821
Taylor, C. *see* Booker, P. D. 365–368
Teiriä, H., Rautoma, P. and Yli-Hankala, A. Effect of smoking on dose requirements for vecuronium 154–155
Tellado, J. M., Forse, R. A. and Solombin, J. S., (editors) *Modulation of the Inflammatory Response in Severe Sepsis*, (*R*) 173–174
Ten Broecke, P. W. *see* Dhirue, G. L., (*EACTA*) A.10
Thalén, P. *see* Nordlander, M., (*EACTA*) A.24
Thämer, V. *see* Schlack, W. 860–867
Thomas, D. *see* Karayan, J. 459–460
Thomas, D. G., Robson, S. C., Redfern, N., Hughes, D. and Boys, R. J. Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for Caesarean section 61–65
Thomas, V. J. and Heath, M. Psychological characteristics and patient-controlled analgesia, (*C*) 595
Thompson, J. P. and Rowbotham, D. J. Remifentanil—an opioid for the 21st century, (*E*) 341–343
Thompson, M. M. and Greiff, J. Aortic stent surgery, (*C*) 883
Thompson, P. *see* Daniell, C. J., (*ARS*) 586–587P
Thorburn, J. *see* Reid, J., (*C*) 335–336
Thornton, C. *see* Brunner, M. D. 34–37; (*C*) 881; Crabb, I. 795–801; Richmond, C. E. 446–448
Thorpe, S. J., Balakrishnan, V. R. and Cook, L. B. Observations on patient-controlled administration of propofol, (*ARS*) 576P
Thorpe, S. J. *see* Smith, A. F., (*ARS*) 577P
Tidmarsh, M. D. Porphyria, propofol and rats, (*C*) 171–172
Timberlake, N. *see* Arowsmith, J. E., (*EACTA*) A.83
Todd, D. B. Histamine release by neuromuscular blocking agents, (*C*) 471
du Toit, J. C. *see* Coetzee, J. F. 415–418
Tomita, M. *see* Denda, S. 258–265
Toner, C. C., Broomhead, C. J., Littlejohn, I. H., Samra, G. S., Powney, J. G., Palazzo, M. G. A., Evans, S. J. W. and Strunin, L. Prediction of postoperative nausea and vomiting using a logistic regression model 347–351
Toraman, F., Kopman, E. A., Çalýþýriþçi, Ü., Demirtaþ, M., Bilgen, F., Özler, A., Canik, S. and Yiðiter, B. Nitroglycerin induced hypoxaemia does not produce myocardial ischaemia, (*EACTA*) A.21
Tormey, W. *see* O'Leary, E. 640–644
Tournadre, J. P., Chassard, D., Berrada, K. R. and Bouletreau, P. Effect of pneumoperitoneum and Trendelenburg position on gastro–oesophageal reflux and lower oesophageal sphincter pressure 130–132
Tramèr, M., Moore, A. and McQuay, H. Omitting nitrous oxide in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials 186–193; Prevention of vomiting after paediatric strabismus surgery, (*C*) 473–474
Tremlett, M. R., Parkins, J., Hughes, D. and Redfern, N. Extradural clonidine provides adjunctive pain relief without sedation for women in labour, (*ARS*) 583–584P
Triggiani, M. *see* Guarracino, F., (*EACTA*) A.45
Tsuneyoshi, I., Kanmura, Y. and Yoshimura, N. Methylprednisolone inhibits endotoxin-induced depression of contractile function in human arteries *in vitro* 251–257
Tullii, M. *see* Casati, V., (*EACTA*) A.53
Tullock, W. *see* De Wolf, A. M. 624–628
Turner, G., Blake, D., Buckland, M., Chamley, D., Dawson, P., Goodchild, C., Mezzatesta, J., Scott, D., Sultana, A., Walker, S., Hendrata, M., Mooney, P. and Armstrong, M. Continuous extradural infusion of ropivacaine for prevention of postoperative pain after major orthopaedic surgery 606–610

Tzabar, Y., Asbury, A. J. and Millar, K. Cognitive failures after general anaesthesia for day-case surgery 194–197

Umbrain, V. *see* Nyarwaya, J.-B. 428–434
Ummenhofer, W. *see* Reber, A., (*ARS*) 584P
Ünal, Ö. *see* Özyurt, A., (*EACTA*) A.25

Vahtera, E. M. *see* Niemi, T. T. 822–828
Valk, R. *see* Dahan, A. 374–381
Valvini, E. M. *see* Young, J. D. 652–656
Van Steenberge, A. L. *see* Vercauteren, M. P. 731–733
Van Aken, H., (editor) *Neuro-anaesthetic Practice*, (*R*) 599
Vandermeersch, E. *see* Van de Velde, M., (*EACTA*) A.3; (*EACTA*) A.4
Van de Velde, M., Wouters, P. F., Laycock, S. K., Leather, A., Leunens, V. and Vandermeersch, E. Long chain triglycerides but not glucose–insulin, administered during reperfusion, improve recovery from stunning in isolated rabbit hearts, (*EACTA*) A.3
Van de Velde, M., Wouters, P. F. and Vandermeersch, E. Oxfenicine blocks the beneficial effects of intravenous long chain triglyceride (LCT) administration on regional myocardial stunning in conscious dogs, (*EACTA*) A.4
Vandommele, J. *see* Meyns, B., (*EACTA*) A.38
VanDyck, M. *see* Deneys, V., (*EACTA*) A.56
Vanlinthout, L. E. H., Booij, L. H. D. J., van Egmond, J. and Robertson, E. N. Effect of isoflurane and sevoflurane on the magnitude and time course of neuromuscular block produced by vecuronium, pancuronium and atracurium 389–395
Van Oldenbeek, C. and Shah, M. V. Relative effects of three hypotensive agents on pulmonary gas exchange, (*EACTA*) A.22
Vasdev, G. M. S. *see* Southorn, P. 467–469
Vaughan, R. S. *see* Asai, T. 772–776
Vebruggen, W. *see* Gouwy, S., (*EACTA*) A.59
Vedrinne, C., Bastien, O., George, M., Durand, P. G., Du Gres, B. and Lehot, J. J. Does Parsonnet score predict the usefulness of Sv_{O_2} pulmonary artery catheter (Sv_{O_2}PAC) during heart surgery? (*EACTA*) A.85
Vedrinne, C., Neidecker, J., Bonnefoy, E., Curtil, A., Ninet, J., Lehot, J. J. and Champsaur, G. Arrhythmias after valvular surgery: a randomized double-blind Holter comparative trial of St Thomas' (ST) *vs* CPS cardioplegia, (*EACTA*) A.66
Vedrinne, C. *see* Lehot, J. J., (*EACTA*) A.43
von der Velde, J. *see* Weyland, A., (*EACTA*) A.35
te Velthuis, H. *see* Jansen, P. G. M. 13–19
Vendrame, G. *see* Oppizzi, M., (*EACTA*) A.46; (*EACTA*) A.81
Venturino, M. *see* Casati, V., (*EACTA*) A.53
Venuti, F. S. *see* Curatolo, M., (*e*) 598
Vercauteren, M. P., Hoffmann, V., Coppejans, H. C., Van Steenberge, A. L. and Adriaensen, H. A. Hydroxyethylstarch compared with modified gelatin as volume preload before spinal anaesthesia for Caesarean section 731–733
Vergroesen, I. *see* van der Stroom, J. G. 645–651
Verhamme, B. *see* Gouwy, S., (*EACTA*) A.59
Vermeulen, H. *see* Versichelen, L. 668–672
Vermeyen, K. M. *see* Deirue, G. L., (*EACTA*) A.10
Vernet, B. *see* Capouet, V. 54–60
Versichelen, L., Rolly, G. and Vermeulen, H. Accumulation of foreign gases during closed-system anaesthesia 668–672
Versichelen, L. *see* Capouet, V. 54–60
Verwaest, C. *see* Meyns, B., (*EACTA*) A.38
Vickers, M. D. *see* Johnston, K. R. 401–404
Vidal, F. *see* Aguilar, J. L. 72–76
Vidal-López, F. *see* Rodríguez-Chinchilla, R. 328–329
Viljoen, J. F. *see* Ruttmann, T. G. 412–414
Villeneuve, E. *see* Lavoie, J., (*EACTA*) A.70
Virtanen, T. *see* Kentala, E., (*EACTA*) A.64
Vischoff, D. *see* Lavoie, J., (*EACTA*) A.70
Visigalli, M. *see* Paino, R., (*EACTA*) A.40
Vlajkovic, G. *see* Sindjelic, R., (*EACTA*) A.19
Vorgrimler-Karzai, U. M. *see* Karzai, W. 5–8
Voyvodic, F. *see* Elliott, D. W. 322–324
Vroom, M. B., Pfaffendorf, M., van Wezel, H. B. and van Zwieten, P. A. Effect of phosphodiesterase inhibitors on human arteries *in vitro* 122–129
Vukotic, A. *see* Sindjelic, R., (*EACTA*) A.19
Vuylsteke, A., Cardan, E., Nyström, P., Latimer, R. and Oduro, A. Effect of aspirin in single first coronary artery bypass grafting, (*EACTA*) A.51
Vuylsteke, A., Feneck, R., Latimer, R., Levy, J., Lynch, C., Ricksten, S.-E., Settergren, G. and Jolin-Mellgård, A. Cardiac surgical practices in the United States of America and Europe: striking similarities and minor differences, (*EACTA*) A.77; Type of perioperative antihypertensive treatment delays extubation and prolongs ICU stay in cardiac surgery, (*EACTA*) A.30
Vuylsteke, A., Guerit, J. M., Dion, R. and Baele, Ph. Evoked potentials challenge the concept of Adamkiewicz's artery, (*EACTA*) A.50

Wadsworth, R. *see* Martlew, R. A. 308–309
Wagenmakers, A. J. M. *see* Pietersen, H. G., (*EACTA*) A.2
Wahren, J. *see* Gårdebäck, M., (*EACTA*) A.36
Walker, S. *see* Turner, G. 606–610
Walpole, A. R. *see* Kitching, A. J. 874–876
Walpoth, B. H., Walpoth, B. N., Eggensperger, N., Neidhart, P., Lanz, M., Spaeth, P., Kurth, G. and Althaus, U. Autologous blood processing during cardiac surgery: haemofiltration *versus* cell washing, (*EACTA*) A.58
Walpoth, B. H., Walpoth, B. N., Mohadjer, A., Gersbach, Ph., Neidhart, P. and Althaus, U. Quality control of coronary bypass surgery: intraoperative transit time flow measurement, (*EACTA*) A.7
Walpoth, B. N. *see* Walpoth, B. H., (*EACTA*) A.7; (*EACTA*) A.58
Wandless, A. L., Smart, D. and Lambert, D. G. Fentanyl increases intracellular Ca^{2+} concentrations in SH-SY5Y cells 461–463
Wang, M. *see* Russell, I. F., (*C*) 884–885
Ward, J. E. H., Caunt, J. A. and Alderson, J. Management of pre-eclampsia, (*C*) 889
Warner, D. O. *see* Fukushima, T. 847–853
Warren, P. M. *see* Foo, I. T. 214–220
Waterloos, H. *see* Deneys, V., (*EACTA*) A.56
Watson., D. *see* Hind, C. J., (*R*) 599
Watt, J. W. H., Fraser, M. H., Soni, B. M., Sett, P. K. and Clay, R. Total i.v. anaesthesia for transcranial magnetic evoked potential spinal cord monitoring 870–871
Webster, N. R. *see* Kulkarni, V., (*ARS*) 586P; Pittard, A. J., (*ARS*) 587P; 629–631
Wegenius, G. *see* Reber, A. 760–766
Weideman, M. M. *see* Daniell, C. J., (*ARS*) 586–587P
Weiss, B. M., Spahn, D. R., Rahmig, H., Rohling, R. and Pasch, T. Radial artery tonometry: moderately accurate but unpredictable technique of continuous non-invasive arterial pressure measurement 405–411
Wellmann, R. *see* Schmidt, H. 707–712
Welte, M., Pichler, B., Groh, J., Anthuber, M., Jauch, K.-W., Pratschke, E., Lenhart, F.-P., Haller, M., Frey, L. and Peter, K. Perioperative mucosal pH and splanchnic endotoxin concentration in orthotopic liver transplantation 90–98
Wernberg, M. *see* Ilkjaer, S. 829–834
West, M. E. and Homi, J. Cannabis as a medicine, (*C*) 167
West, M. R. J., Jonas, M. M., Adams, A. P. and Carli, F. A new tracheal tube for difficult intubation 673–679
Westerlind, A. *see* Ederberg, S., (*EACTA*) A.17
Weterings, C. J., Prinzen, F. W., Reneman, R. S. and de Lange, S. The effect of the calcium sensitizer levosimendan on normal and stunned left ventricular myocardium, (*EACTA*) A.8
Wetselaar, K. E. *see* Boer, F. 203–208
Weyland, A., Grüne, F., Stephan, H., von der Velde, J., Kazmaier, S. and Sonntag, H. Cerebral blood flow response to changes in CO_2 at hypothermia and normothermia. A controlled, randomized crossover study, (*EACTA*) A.35
Weyland, A. *see* Buhre, W., (*EACTA*) A.37; Kazmaier, S., (*EACTA*) A.5
van Wezel, H. B. *see* van der Stroom, J. G. 645–651; Vroom, M. B. 122–129
Wheeldon, D. *see* Dhond, G., (*EACTA*) A.57
Wheildon, M. *see* Brosnan, C. M., (*C*) 887–888
White, D. *see* Royston, B., (*ARS*) 582–583P
White, D. C. *see* Pal, S. K., (*ARS*) 582P
White, P. F. *see* Smith, I. 435–445
Wierda, J. M. K.H. *see* Beaufort, A. M., (*ARS*) 580P
Wierda, J. M. K. H. *see* McCoy, E. P. 29–33
Wiesner, G. *see* Rödig, G. 9–12
Wilder-Smith, O. H. G., Hagon, O. and Tassonyi, E. EEG arousal during laryngoscopy and intubation, (*C*) 472–473
Wilder-Smith, O. H. G., Tassonyi, E., Senly, C., Otten, Ph. and Arendt-Nielsen, L. Surgical pain is followed not only by spinal sensitization but also by supraspinal antinociception 816–821
Wildevuur, C. R. H. *see* Jansen, P. G. M. 13–19
Wildevuur, W. R. *see* Jansen, P. G. M. 13–19

Wilkes, A. R. and Mapleson, W. W. Interference of volatile anaesthetics with infrared analysis of carbon dioxide and nitrous oxide tested in the Dräger Cicero EM using sevoflurane 737–739
Williams, N. J. *see* Myles, P. S. 694–698
Williams, P. I. Naproxen after day-case laparoscopic sterilization, (*C*) 168
Williams, T. B. *see* Galletly, D. C. 503–507
Williamson, K. *see* Mushambi, M. C. 133–148; (*C*) 889–890
Williger, H. M. M., Prinzen, F. W. and de Lange, S. A comparison of the limitation of sympathetic responses by β_1-blocker esmolol and α_2-adrenergic agonist dexmedetomidine, (*EACTA*) A.23
Wilson, A. J., Diemunsch, P., Lindeque, B. G., Scheinin, H., Helbo-Hansen, H. S., Kroeks, M. V. A.M. and Kong, K. L. Single-dose i.v. granisetron in the prevention of postoperative nausea and vomiting 515–518
Wilson, J. A. Cardiac arrest at induction of anaesthesia for Caesarean section, (*C*) 332
Wilson, R. *see* Hawthorne, L. 680–684
Wiltshire, S. *see* Driver, I., (*e*) 175
Wintrebert, P. *see* Calvert, B., (*EACTA*) A.78; Ryckwaert, F., (*EACTA*) A.34
Wirtavuori, K. *see* Meretoja, O. A. 235–238; 767–771
Wislocki, W. *see* Mares, P., (*EACTA*) A.75
Wisnewski, J. *see* Corbett, A. R., (*ARS*) 593–594P
Wojtalik, M. *see* Knapik, P., (*EACTA*) A.28
Wolf, A. R., Lawson, R. A., Dryden, C. M. and Davies, F. W. Recovery after desflurane anaesthesia in the infant: comparison with isoflurane 362–364
Wolf, A. R. *see* Hughes, D. G., (*R*) 599
Wood, M. L. B. *see* Brosnan, C. M., (*C*) 887–888
Wood, P. R. and Lawler, P. G. P. Measurement technique and variation in intramucosal pH 563–564
Woolman, P. *see* Smith, E., (*EACTA*) A.86
Wouters, P. *see* Gouwy, S., (*EACTA*) A.59
Wouters, P. F. *see* Van de Velde, M., (*EACTA*) A.3; (*EACTA*) A.4
Wraith, P. K. *see* Spens, H. J. 369–373
Wright, J. S. *see* Davis, G. 879–880
Wulf, H. *see* Smith, T. 452–455
Wyatt, J. S. *see* Owen-Reece, H. 43–48

Yamakura, T. *see* Denda, S. 258–265
Yapýcý, F. *see* Özyurt, A., (*EACTA*) A.25
Yiðiter, B. *see* Toraman, F., (*EACTA*) A.21
Yli-Hankala, A. *see* Hammarén, E., (*EACTA*) A.16; Teiriä, H. 154–155
Yoshimura, N. *see* Tsuneyoshi, I. 251–257
Young, J. D., Sear, J. W. and Valvini, E. M. Kinetics of methaemoglobin and serum nitrogen oxide production during inhalation of nitric oxide in volunteers 652–656
Young, Y. *see* Bellamy, M. C., (*ARS*) 587P; Snook, N. J. 740–743
Yurtseven, N. *see* Özyurt, A., (*EACTA*) A.25

Zacharias, M. *see* Joyce, C. J. 292–296
Zbinden, A. M. *see* Curatolo, M. 245–250; (*e*) 598; Roth, D. 38–42
Zhang, X. *see* Lee, C. 278–283
Zoia, E. *see* Oppizzi, M., (*EACTA*) A.46
Zsigmond, E. K. *see* Hirota, K. 266–270
Züchner, K. *see* Kazmaier, S., (*EACTA*) A.5
Zurschmiede, C. *see* Reber, A., (*ARS*) 584P
van Zwieten, P. A. *see* van der Stroom, J. G. 645–651; Vroom, M. B. 122–129
Zych, Z. *see* Pal, S. K., (*ARS*) 582P

SUBJECT INDEX

A Physicians's Guide to the Internet, Hancock, L., (*R*) 893

A Practical Approach to Cardiac Anesthesia, Hensley, F. A. jr, *et al.*, (editors), (*R*) 174

ACE inhibitor, Hypotension following the administration of fentanyl-diazepam combination in chronic ACE inhibitor users, Özyurt, A., *et al.*, (*EACTA*) A.25

Acid–base equilibrium, pH, Gastric tonometry, Boyd, O., *et al.*, (*C*) 750

Acute Pain Management: A Practical Guide, Macintyre, P. E., *et al.*, (*R*) 892

Adolescents, Anatomical configuration of the spinal column in the supine position. III. Comparison of adolescent and adult volunteers, Hirabayashi, Y., *et al.* 508–510

Age factors, Anatomical configuration of the spinal column in the supine position. III. Comparison of adolescent and adult volunteers, Hirabayashi, Y., *et al.* 508–510

——, Effect of age on MAC in humans: a meta-analysis, Mapleson, W. W. 179–185

Air ambulance, Haemodynamic effects of air travel, Malagon, I., (*ARS*) 590P

Airway, Evaluation of an oesophageal intubation detector device using electrical resistance, Deakin, C. D., (*ARS*) 590P

Airway, calibre, A novel fibreoptic pressure transducer system for the upper airway, Secker, C., *et al.*, (*ARS*) 581–582P

Airway, complications, A novel fibreoptic pressure transducer system for the upper airway, Secker, C., *et al.*, (*ARS*) 581–582P

Airway, muscles, Comparison of sedation with midazolam and ketamine: effects on airway muscle activity, Drummond, G. B. 663–667

——, Differential effects of desflurane and halothane on peripheral airway smooth muscle, Mazzeo, A. J., *et al.* 841–846

——, Halothane and potassium channels in airway smooth muscle, Fukushima, T., *et al.* 847–853

——, Relaxant effect of ketamine and its isomers on histamine-induced contraction of tracheal smooth muscle, Hirota, K., *et al.* 266–270

Airway, obstruction, Airway problems after carotid endarterectomy, Munro, F. J., *et al.* 156–159

——, Cervical haematoma and airway obstruction, Calder, I., *et al.*, (*C*) 888

——, Cervical haematoma and airway obstruction, Munro, F. J., *et al.*, (*C*) 888–889

Airway, pressure, Airway pressure signals during high frequency jet ventilation, Lin, E. S., (*ARS*) 576–577P

——, Magnetic resonance imaging of the superior vena cava during spontaneous respiration with continuous positive airway pressure via a facemask in normal subjects, Mayor, A. H., *et al.*, (*ARS*) 578–579P

Anaesthesia, Effect of anaesthetic agents on pulmonary shunt during coronary artery surgery, Sindjelic, R., *et al.*, (*EACTA*) A.19

——, Hypotension following the administration of fentanyl-diazepam combination in chronic ACE inhibitor users, Özyurt, A., *et al.*, (*EACTA*) A.25

Anaesthesia and Critical Care Manual, 2nd Edn, Cunningham, A. J., (editor), (*R*) 338

Anaesthesia, audit, A pitfall in the use of the Altman nomogram for power estimation, Evans, M. J., *et al.*, (*C*) 334

——, Cost of volatile agents, Barker, I., (*C*) 749

——, Economy during induction of anaesthesia: a comparison of desflurane with isoflurane via a circle system, Pal, S. K., *et al.*, (*ARS*) 582P

——, Measurement of competence, Goodman, N. W., (*C*) 750

——, Omitting nitrous oxide in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials, Tramèr, M., *et al.* 186–193

——, Prehospital monitoring of trauma patients: experience of a helicopter emergency medical service, Morley, A. P. 726–730

Anaesthesia, day-case, Cognitive failures after general anaesthesia for day-case surgery, Tzabar, Y., *et al.* 194–197

——, Day-case cataract surgery, Goold, J. E., (*C*) 333

——, Day-case cataract surgery, Maltby, J. R., *et al.*, (*C*) 333

——, Naproxen after day-case laparoscopic sterilization, Dunn, T. J., *et al.*, (*C*) 168

——, Naproxen after day-case laparoscopic sterilization, Williams, P. I., (*C*) 168

——, Regional anaesthesia for outpatient nasal surgery, Molliex, S., *et al.* 151–153

Anaesthesia, depth, Double-blind, randomized trial of cessation of smoking after audiotape suggestion during anaesthesia, Myles, P. S., *et al.* 694–698

——, EEG arousal during laryngoscopy and intubation, Shannon, C., *et al.*, (*C*) 472

——, EEG arousal during laryngoscopy and intubation, Wilder-Smith, O. H. G., *et al.*, (*C*) 472–473

——, Effect of neuromuscular block on depth of anaesthesia as measured by the auditory evoked response, Richmond, C. E., *et al.* 446–448

——, Effect of tramadol on depth of anaesthesia, Coetzee, J. F., *et al.* 415–418

——, Heart rate variability in patients recovering from general anaesthesia, Ireland, N., *et al.* 657–662

——, Is there implicit memory after propofol sedation? Cork, R. C., *et al.* 492–498

——, Isolated forearm technique, Healy, T. E. J., *et al.*, (*C*) 885–886

——, Isolated forearm technique, Russell, I. F., *et al.*, (*C*) 884–885

——, Omitting nitrous oxide in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials, Tramèr, M., *et al.* 186–193

——, Recall during intermittent propofol anaesthesia, Nordström, O., *et al.* 699–701

Anaesthesia, emergency service, Prehospital monitoring of trauma patients: experience of a helicopter emergency medical service, Morley, A. P. 726–730

Anaesthesia for Surgery of the Spine, Porter, S. S., (editor), (*R*) 892

Anaesthesia, general, Changes in pineal and pituitary hormone secretion under general anaesthesia, Reber, A., *et al.*, (*ARS*) 584P

——, Heart rate variability in patients recovering from general anaesthesia, Ireland, N., *et al.* 657–662

——, Midazolam before induction improves conditions for laryngeal mask insertion, Driver, I., *et al.*, (*e*) 175

——, Volumetric analysis of aeration in the lungs during general anaesthesia, Reber, A., *et al.* 760–766

Anaesthesia, geriatric, Day-case cataract surgery, Goold, J. E., (*C*) 333

——, Day-case cataract surgery, Maltby, J. R., *et al.*, (*C*) 333

Anaesthesia, journals, Impact factors in anaesthesia journals, Smith, G., (*E*) 753–754

——, The 11th World Congress of Anaesthesiology, Smith, G., (*E*) 479–480

Anaesthesia, obstetric, A double-blind comparison of 0.25% ropivacaine and 0.25% bupivacaine for extradural analgesia in labour, Eddleston, J. M., *et al.* 66–71

——, Accidental insertion of an extradural catheter, Fox, A., *et al.*, (*C*) 336

——, Cardiac arrest at induction of anaesthesia for Caesarean section, McIndoe, A. K., *et al.*, (*C*) 332–333

——, Cardiac arrest at induction of anaesthesia for Caesarean section, Wilson, J. A., (*C*) 332

——, CSF progesterone concentrations in pregnancy, Baliga, N., (*C*) 886

——, CSF progesterone concentrations in pregnancy, Hirabayashi, Y., *et al.*, (*C*) 886

——, Elective forceps delivery and extradural anaesthesia in a primigravida with portal hypertension and oesophageal varices, Heriot, J. A., *et al.* 325–327

——, Failed intubation revisited: 17-yr experience in a teaching maternity unit, Hawthorne, L., *et al.* 680–684

——, Hydroxyethylstarch compared with modified gelatin as volume preload before spinal anaesthesia for Caesarean section, Vercauteren, M. P., *et al.* 731–733
——, Intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia, Camann, W., (*C*) 169
——, Intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia, Lee, J. S., *et al.*, (*C*) 169–170
——, Intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia, Robbins, P. M., *et al.*, (*C*) 170
——, Maternal and uteroplacental haemodynamic state in pre-eclamptic patients during spinal anaesthesia for Caesarean section, Karinen, J., *et al.* 616–620
——, Patient-controlled extradural analgesia with bupivacaine, fentanyl, or a mixture of both, after Caesarean section, Cooper, D. W., *et al.* 611–615
——, Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for Caesarean section, Thomas, D. G., *et al.* 61–65
——, Spinal anaesthesia for Caesarean section in women with incomplete extradural analgesia, Stoneham, M., *et al.*, (*C*) 476
——, Sudden onset of subarachnoid block after subdural catheterization: a case of arachnoid rupture? Elliott, D. W., *et al.* 322–324
——, Visceral pain during Caesarean section, Fairfield, M. C., (*C*) 167
——, Visceral pain during Caesarean section, Hirabayashi, Y., *et al.*, (*C*) 167
——, Volume preloading, spinal anaesthesia and Caesarean section, Lawes, E. G., (*C*) 334–335
——, Volume preloading, spinal anaesthesia and Caesarean section, Mallick, A., *et al.*, (*C*) 335
——, Volume preloading, spinal anaesthesia and Caesarean section, Reid, J., *et al.*, (*C*) 335–336
Anaesthesia, paediatric, Airway management in cleft lip and palate surgery, Hatch, D. J., (*E*) 755–756
——, Anaesthesia and juvenile hyaline fibromatosis, Norman, B., *et al.* 163–166
——, Continuous extrapleural paravertebral infusion of bupivacaine for post-thoracotomy analgesia in young infants, Karmakar, M. K., *et al.* 811–815
——, Difficult laryngoscopy in cleft lip and palate surgery, Gunawardana, R. H. 757–759
——, Dose of propofol for laryngeal mask airway insertion in children: effect of premedication with midazolam, Martlew, R. A., *et al.* 308–309
——, Parental or anaesthetist's ability to predict a 'stormy' induction in young children, Lyons, B., *et al.*, (*ARS*) 589P
——, Perioperative changes in α_1-acid glycoprotein concentrations in infants undergoing major surgery, Booker, P. D., *et al.* 365–368
——, Preoperative fasting for paediatric anaesthesia, Hopp, M., (*C*) 471
——, Preoperative fasting for paediatric anaesthesia, Phillips, S., *et al.*, (*C*) 471
——, Recovery after desflurane anaesthesia in the infant: comparison with isoflurane, Wolf, A. R., *et al.* 362–364
——, Removal of the laryngeal mask airway in children: anaesthetized compared with awake, Kitching, A. J., *et al.* 874–876
——, Sevoflurane–nitrous oxide or halothane–nitrous oxide for paediatric bronchoscopy and gastroscopy, Meretoja, O. A., *et al.* 767–771
——, Smaller children have greater bupivacaine plasma concentrations after ilioinguinal block, Smith, T., *et al.* 452–455
Anaesthesia: Review 11, Kaufman, L., *et al.*, (editors), (*R*) 174
Anaesthetic techniques, extradural, A double-blind comparison of 0.25% ropivacaine and 0.25% bupivacaine for extradural analgesia in labour, Eddleston, J. M., *et al.* 66–71
——, A multifactorial analysis to explain inadequate surgical analgesia after extradural block, Curatolo, M., *et al.*, (*e*) 598
——, Accidental insertion of an extradural catheter, Fox, A., *et al.*, (*C*) 336
——, Continuous extradural infusion of ropivacaine for prevention of postoperative pain after major orthopaedic surgery, Turner, G., *et al.* 606–610
——, Does pre-incisional thoracic extradural block combined with diclofenac reduce postoperative pain after abdominal hysterectomy? Espinet, A., *et al.* 209–213
——, Elective forceps delivery and extradural anaesthesia in a primigravida with portal hypertension and oesophageal varices, Heriot, J. A., *et al.* 325–327
——, Extradural analgesia in the first stage of labour, Buggy, D., *et al.*, (*C*) 887
——, Extradural analgesia in the first stage of labour, Fernando, R., *et al.*, (*C*) 886–887
——, Extradural analgesia with clonidine and fentanyl compared with 0.25% bupivacaine in the first stage of labour, Buggy, D. J., *et al.* 319–321
——, Extradurals and infection, Brosnan, C. M., *et al.*, (*C*) 887–888
——, Inadvertent infusion of glucose saline into the extradural space, Mphanza, T., (*C*) 332
——, Intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia, Camann, W., (*C*) 169
——, Intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia, Lee, J. S., *et al.*, (*C*) 169–170
——, Intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia, Robbins, P. M., *et al.*, (*C*) 170
——, Patient-controlled extradural analgesia with bupivacaine, fentanyl, or a mixture of both, after Caesarean section, Cooper, D. W., *et al.* 611–615
——, Postoperative analgesia by continuous extradural infusion of ropivacaine after upper abdominal surgery, Schug, S. A., *et al.* 487–491
——, Reducing the potential morbidity of an unintentional spinal anaesthetic by aspirating cerebrospinal fluid, Southorn, P., *et al.* 467–469
——, Spinal anaesthesia for Caesarean section in women with incomplete extradural analgesia, Stoneham, M., *et al.*, (*C*) 476
——, Sudden onset of subarachnoid block after subdural catheterization: a case of arachnoid rupture? Elliott, D. W., *et al.* 322–324
——, Ventilatory response to carbon dioxide, Dahan, A., *et al.*, (*C*) 747
——, Ventilatory response to carbon dioxide, Saito, Y., *et al.*, (*C*) 747–748
Anaesthetic techniques, extubation, Haemodynamic effects of continued sedation during tracheal extubation, Conti, J., *et al.*, (*EACTA*) A.72
Anaesthetic techniques, hypotensive, Metabolic and hormonal responses to induced hypotension for middle ear surgery, Newton, M. C., *et al.* 352–357
Anaesthetic techniques, hypotensive, nitroprusside, Haemodynamic effects of sodium nitroprusside *versus* prostaglandin E_1 in heart transplant candidates, Coddens, J., *et al.*, (*EACTA*) A.26
Anaesthetic techniques, induction, EEG arousal during laryngoscopy and intubation, Shannon, C., *et al.*, (*C*) 472
——, EEG arousal during laryngoscopy and intubation, Wilder-Smith, O. H. G., *et al.*, (*C*) 472–473
Anaesthetic techniques, i.v., Prospective evaluation of pharmacokinetic model-controlled infusion of propofol in adult patients, Short, T. G., *et al.* 313–315
Anaesthetic techniques, laryngoscopy, Airway management in cleft lip and palate surgery, Hatch, D. J., (*E*) 755–756
——, Difficult laryngoscopy in cleft lip and palate surgery, Gunawardana, R. H. 757–759
——, EEG arousal during laryngoscopy and intubation, Shannon, C., *et al.*, (*C*) 472
——, EEG arousal during laryngoscopy and intubation, Wilder-Smith, O. H. G., *et al.*, (*C*) 472–473
Anaesthetic techniques, low flow, Fuzzy logic control of inspired isoflurane and oxygen concentrations using minimal flow anaesthesia, Curatolo, M., *et al.* 245–250
Anaesthetic techniques, preoxygenation, Improving preoxygenation, McGowan, P., (*C*) 748
——, Improving preoxygenation, Smith, A. F., (*C*) 748
Anaesthetic techniques, regional, Haemostatic changes caused by i.v. regional anaesthesia with lignocaine, Niemi, T. T., *et al.* 822–828
——, Isolated forearm technique, Healy, T. E. J., *et al.*, (*C*) 885–886
——, Isolated forearm technique, Russell, I. F., *et al.*, (*C*) 884–885
——, Regional anaesthesia for outpatient nasal surgery, Molliex, S., *et al.* 151–153
——, Ulnar and common peroneal nerve block revisited, Souter, A. J., *et al.*, (*C*) 595–596
Anaesthetic techniques, regional, brachial plexus, Effect of the addition of alfentanil to lignocaine during axillary brachial plexus anaesthesia, Gormley, W. P., *et al.* 802–805

Anaesthetic techniques, regional, inguinal, Smaller children have greater bupivacaine plasma concentrations after ilioinguinal block, Smith, T., *et al.* 452–455
Anaesthetic techniques, regional, interpleural, Interpleural local anaesthesia: anatomical basis for mechanism of action, McKenzie, A. G., *et al.* 297–299
Anaesthetic techniques, regional, paravertebral, Continuous extrapleural paravertebral infusion of bupivacaine for post-thoracotomy analgesia in young infants, Karmakar, M. K., *et al.* 811–815
Anaesthetic techniques, regional, peribulbar, Prilocaine 3% is superior to a mixture of bupivacaine and lignocaine for peribulbar anaesthesia, Döpfmer, U. R., *et al.* 77–80
Anaesthetic techniques, subarachnoid, Accidental insertion of an extradural catheter, Fox, A., *et al.*, (*C*) 336
——, Anatomical configuration of the spinal column in the supine position. III. Comparison of adolescent and adult volunteers, Hirabayashi, Y., *et al.* 508–510
——, Bilateral severe pain at L3–4 after spinal anaesthesia with hyperbaric 5% lignocaine, Rodríguez-Chinchilla, R., *et al.* 328–329
——, CSF progesterone concentrations in pregnancy, Baliga, N., (*C*) 886
——, CSF progesterone concentrations in pregnancy, Hirabayashi, Y., *et al.*, (*C*) 886
——, Extradural and subarachnoid catheterization using the Seldinger technique, Delhaas, E. M. 149–150
——, Hydroxyethylstarch compared with modified gelatin as volume preload before spinal anaesthesia for Caesarean section, Vercauteren, M. P., *et al.* 731–733
——, Hypotension during subarachnoid anaesthesia: haemodynamic effects of colloid and metaraminol, Critchley, L. A. H., *et al.* 734–736
——, Intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia, Camann, W., (*C*) 169
——, Intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia, Lee, J. S., *et al.*, (*C*) 169–170
——, Intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia, Robbins, P. M., *et al.*, (*C*) 170
——, Maternal and uteroplacental haemodynamic state in pre-eclamptic patients during spinal anaesthesia for Caesarean section, Karinen, J., *et al.* 616–620
——, Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for Caesarean section, Thomas, D. G., *et al.* 61–65
——, Spinal anaesthesia for Caesarean section in women with incomplete extradural analgesia, Stoneham, M., *et al.*, (*C*) 476
——, Spinal clonidine produces less urinary retention than spinal morphine, Gentili, M., *et al.* 872–873
——, Visceral pain during Caesarean section, Fairfield, M. C., (*C*) 167
——, Visceral pain during Caesarean section, Hirabayashi, Y., *et al.*, (*C*) 167
——, Volume preloading, spinal anaesthesia and Caesarean section, Lawes, E. G., (*C*) 334–335
——, Volume preloading, spinal anaesthesia and Caesarean section, Mallick, A., *et al.*, (*C*) 335
——, Volume preloading, spinal anaesthesia and Caesarean section, Reid, J., *et al.*, (*C*) 335–336
Anaesthetic techniques, topical, nitroglycerine, Nitroglycerin induced hypoxaemia does not produce myocardial ischaemia, Toraman, F., *et al.*, (*EACTA*) A.21
——, Topical nitroglycerin dilates the radial artery, Gota, M., *et al.*, (*EACTA*) A.20
Anaesthetics gases, Effect of age on MAC in humans: a meta-analysis, Mapleson, W. W. 179–185
Anaesthetics gases, nitrous oxide, Auditory evoked responses, median frequency and 95% spectral edge during anaesthesia with desflurane and nitrous oxide, Pal, S. K., *et al.*, (*ARS*) 577P
——, Effects of carbon dioxide embolism with nitrous oxide in the inspired gas in piglets, Nyarwaya, J.-B., *et al.* 428–434
——, Nitrous oxide and the rate of gas uptake from an unventilated lung in dogs, Joyce, C. J., *et al.* 292–296
——, Nitrous oxide or halothane, or both, fail to suppress c-*fos* expression in rat spinal cord dorsal horn neurones after subcutaneous formalin, Sun, W. Z., *et al.* 99–105
——, Omitting nitrous oxide in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials, Tramèr, M., *et al.* 186–193
——, Volatile anaesthetics antagonize nitrous oxide and morphine-induced analgesia in the rat, Goto, T., *et al.* 702–706
Anaesthetics i.v., Flow cytometry evaluation of the *in vitro* effects of four i.v. anaesthetics on the respiratory burst of human neutrophils, Leuwer, M., *et al.*, (*ARS*) 585P
——, Interaction of i.v. anaesthetic agents with 5-HT_3 receptors, Appadu, B. L., *et al.* 271–273
——, Is the dihydropyridine binding site on neuronal L-type calcium channels a target for i.v. anaesthetic agents? Hirota, K., *et al.*, (*ARS*) 591P
——, Org 21465 a new i.v. anaesthetic agent, Daniell, C. J., *et al.*, (*ARS*) 586–587P
——, Total i.v. anaesthesia for transcranial magnetic evoked potential spinal cord monitoring, Watt, J. W. H., *et al.* 870–871
Anaesthetics i.v., eltanolone, Changes in chest wall compartment volumes on induction of anaesthesia with eltanolone, propofol and thiopentone, Spens, H. J., *et al.* 369–373
Anaesthetics i.v., etomidate, Day-case cataract surgery, Goold, J. E., (*C*) 333
——, Day-case cataract surgery, Maltby, J. R., *et al.*, (*C*) 333
Anaesthetics i.v., fentanyl, Nitrous oxide or halothane, or both, fail to suppress c-*fos* expression in rat spinal cord dorsal horn neurones after subcutaneous formalin, Sun, W. Z., *et al.* 99–105
Anaesthetics i.v., ketamine, Central nuclei and spinal pathways in feedback inhibitory spinal cord potentials in ketamine-anaesthetized rats, Denda, S., *et al.* 258–265
——, Comparison of sedation with midazolam and ketamine: effects on airway muscle activity, Drummond, G. B. 663–667
——, Effect of systemic *N*-methyl-D-aspartate receptor antagonist (ketamine) on primary and secondary hyperalgesia in humans, Ilkjaer, S., *et al.* 829–834
——, Relaxant effect of ketamine and its isomers on histamine-induced contraction of tracheal smooth muscle, Hirota, K., *et al.* 266–270
Anaesthetics i.v., propofol, A perfusion system for *in vitro* measurement of human cilia beat frequency, Selwyn, D. A., *et al.* 111–115
——, Activation of the electrocorticogram by propofol during surgery for epilepsy, Smith, M., *et al.* 499–502
——, Changes in chest wall compartment volumes on induction of anaesthesia with eltanolone, propofol and thiopentone, Spens, H. J., *et al.* 369–373
——, Comparison of arterialized venous with arterial blood propofol concentrations during sub-anaesthetic infusions in volunteers, Johnston, K. R., *et al.* 401–404
——, Day-case cataract surgery, Goold, J. E., (*C*) 333
——, Day-case cataract surgery, Maltby, J. R., *et al.*, (*C*) 333
——, Does propofol change the phenotype of monocytes in thoracic surgery? Laßnigg, A., *et al.*, (*EACTA*) A.18
——, Dose of propofol for laryngeal mask airway insertion in children: effect of premedication with midazolam, Martlew, R. A., *et al.* 308–309
——, EEG arousal during laryngoscopy and intubation, Shannon, C., *et al.*, (*C*) 472
——, EEG arousal during laryngoscopy and intubation, Wilder-Smith, O. H. G., *et al.*, (*C*) 472–473
——, Effect of propofol and thiopentone on free radical mediated oxidative stress of the erythrocyte, Murphy, P. G., *et al.* 536–543
——, Effects of propofol and isoflurane on right ventricular function, Boyd, O., *et al.*, (*C*) 598
——, Effects of propofol on rabbit mesenteric arteries and veins, Kamitani, K., (*C*) 333–334
——, Effects of propofol on rabbit mesenteric arteries and veins, Stratford, N., (*C*) 333
——, Investigation into the effects of midazolam and propofol on human respiratory cilia beat frequency *in vitro*, Hann, H. C. L., *et al.*, (*ARS*) 591P
——, Is there implicit memory after propofol sedation? Cork, R. C., *et al.* 492–498
——, Midazolam before induction improves conditions for laryngeal mask insertion, Driver, I., *et al.*, (*e*) 175
——, Patient-controlled propofol: randomized, double-blind dose refinement, Smith, A. F., *et al.*, (*ARS*) 577P
——, Plasma concentration and protein binding of propofol during cardiac surgery, Hammarén, E., *et al.*, (*EACTA*) A.16
——, Porphyria, propofol and rats, Böhrer, H., (*C*) 172
——, Porphyria, propofol and rats, Gorchein, A., (*C*) 172
——, Porphyria, propofol and rats, Tidmarsh, M. D., (*C*) 171–172
——, Prospective evaluation of pharmacokinetic model-controlled infusion of propofol in adult patients, Short, T. G., *et al.* 313–315
——, Recall during intermittent propofol anaesthesia, Nordström, O., *et al.* 699–701
——, The effects of propofol on cerebral blood flow velocity

and oxygenation during cardiopulmonary bypass, Ederberg, S., *et al.*, (*EACTA*) A.17

——, Unilateral convulsion after induction of anaesthesia with propofol, Cochran, D., *et al.* 570–572

Anaesthetics i.v., thiopentone, Changes in chest wall compartment volumes on induction of anaesthesia with eltanolone, propofol and thiopentone, Spens, H. J., *et al.* 369–373

——, EEG arousal during laryngoscopy and intubation, Shannon, C., *et al.*, (*C*) 472

——, EEG arousal during laryngoscopy and intubation, Wilder-Smith, O. H. G., *et al.*, (*C*) 472–473

——, Effect of propofol and thiopentone on free radical mediated oxidative stress of the erythrocyte, Murphy, P. G., *et al.* 536–543

Anaesthetics local, amethocaine, CSF progesterone concentrations in pregnancy, Baliga, N., (*C*) 886

——, CSF progesterone concentrations in pregnancy, Hirabayashi, Y., *et al.*, (*C*) 886

——, Visceral pain during Caesarean section, Fairfield, M. C., (*C*) 167

——, Visceral pain during Caesarean section, Hirabayashi, Y., *et al.*, (*C*) 167

Anaesthetics local, bupivacaine, A double-blind comparison of 0.25% ropivacaine and 0.25% bupivacaine for extradural analgesia in labour, Eddleston, J. M., *et al.* 66–71

——, Absence of an early pre-emptive effect after thoracic extradural bupivacaine in thoracic surgery, Aguilar, J. L., *et al.* 72–76

——, Continuous extrapleural paravertebral infusion of bupivacaine for post-thoracotomy analgesia in young infants, Karmakar, M. K., *et al.* 811–815

——, Extradural analgesia in the first stage of labour, Buggy, D., *et al.*, (*C*) 887

——, Extradural analgesia in the first stage of labour, Fernando, R., *et al.*, (*C*) 886–887

——, Extradural analgesia with clonidine and fentanyl compared with 0.25% bupivacaine in the first stage of labour, Buggy, D. J., *et al.* 319–321

——, Extradural clonidine for postoperative pain relief, Nishikawa, T., (*C*) 171

——, Patient-controlled extradural analgesia with bupivacaine, fentanyl, or a mixture of both, after Caesarean section, Cooper, D. W., *et al.* 611–615

——, Prilocaine 3% is superior to a mixture of bupivacaine and lignocaine for peribulbar anaesthesia, Döpfmer, U. R., *et al.* 77–80

——, Smaller children have greater bupivacaine plasma concentrations after ilioinguinal block, Smith, T., *et al.* 452–455

Anaesthetics local, EMLA, Analgesic and anti-inflammatory effects of lignocaine–prilocaine (EMLA) cream in human burn injury, Pedersen, J. L., *et al.* 806–810

Anaesthetics local, lignocaine, Bilateral severe pain at L3–4 after spinal anaesthesia with hyperbaric 5% lignocaine, Rodríguez-Chinchilla, R., *et al.* 328–329

——, Effect of the addition of alfentanil to lignocaine during axillary brachial plexus anaesthesia, Gormley, W. P., *et al.* 802–805

——, Haemostatic changes caused by i.v. regional anaesthesia with lignocaine, Niemi, T. T., *et al.* 822–828

——, Nebulized lignocaine before gaseous induction with desflurane, Bunting, H. E., *et al.*, (*C*) 596

——, Nebulized lignocaine before gaseous induction with desflurane, Nay, P. G., (*C*) 596

——, Prilocaine 3% is superior to a mixture of bupivacaine and lignocaine for peribulbar anaesthesia, Döpfmer, U. R., *et al.* 77–80

——, Ventilatory response to carbon dioxide, Dahan, A., *et al.*, (*C*) 747

——, Ventilatory response to carbon dioxide, Saito, Y., *et al.*, (*C*) 747–748

Anaesthetics local, prilocaine, Prilocaine 3% is superior to a mixture of bupivacaine and lignocaine for peribulbar anaesthesia, Döpfmer, U. R., *et al.* 77–80

Anaesthetics local, ropivacaine, A double-blind comparison of 0.25% ropivacaine and 0.25% bupivacaine for extradural analgesia in labour, Eddleston, J. M., *et al.* 66–71

——, Continuous extradural infusion of ropivacaine for prevention of postoperative pain after major orthopaedic surgery, Turner, G., *et al.* 606–610

——, Postoperative analgesia by continuous extradural infusion of ropivacaine after upper abdominal surgery, Schug, S. A., *et al.* 487–491

——, Ropivacaine, McClure, J. H. 300–307

Anaesthetics volatile, Cost of volatile agents, Barker, I., (*C*) 749

——, Effect of age on MAC in humans: a meta-analysis, Mapleson, W. W. 179–185

——, Interference of volatile anaesthetics with infrared analysis of carbon dioxide and nitrous oxide tested in the Dräger Cicero EM using sevoflurane, Wilkes, A. R., *et al.* 737–739

——, Remembrance of times past: the significance of c-*fos* in pain, Munglani, R., *et al.*, (*E*) 1–4

Anaesthetics volatile, desflurane, Auditory evoked responses, median frequency and 95% spectral edge during anaesthesia with desflurane and nitrous oxide, Pal, S. K., *et al.*, (*ARS*) 577P

——, Differential effects of desflurane and halothane on peripheral airway smooth muscle, Mazzeo, A. J., *et al.* 841–846

——, Economy during induction of anaesthesia: a comparison of desflurane with isoflurane via a circle system, Pal, S. K., *et al.*, (*ARS*) 582P

——, Effects of desflurane and isoflurane on splanchnic microcirculation during surgery, O'Beirne, H., *et al.*, (*ARS*) 592P

——, Efficiency of a circle system for short surgical cases: comparison of desflurane with isoflurane, Lee, D. J. H., *et al.* 780–782

——, Nebulized lignocaine before gaseous induction with desflurane, Bunting, H. E., *et al.*, (*C*) 596

——, Nebulized lignocaine before gaseous induction with desflurane, Nay, P. G., (*C*) 596

——, Recovery after desflurane anaesthesia in the infant: comparison with isoflurane, Wolf, A. R., *et al.* 362–364

Anaesthetics volatile, enflurane, Effects of 3 MAC of halothane, enflurane and isoflurane on cilia beat frequency of human nasal epithelium *in vitro*, Raphael, J. H., *et al.* 116–121

——, Effects of surgical skin incision on respiration in patients anaesthetized with enflurane, Sutherland, R. W., *et al.* 777–779

——, Recovery of respiratory ciliary function after depression by inhalation anaesthetic agents: an *in vitro* study using nasal turbinate explants, Raphael, J. H., *et al.* 854–859

——, Sevoflurane, enflurane and isoflurane have no persistent postanaesthetic effects on the central nervous system in cats, Kurata, J., *et al.* 721–725

Anaesthetics volatile, halothane, Differential effects of desflurane and halothane on peripheral airway smooth muscle, Mazzeo, A. J., *et al.* 841–846

——, Effect of halothane on myocardial reoxygenation injury in the isolated rat heart, Schlack, W., *et al.* 860–867

——, Effects of 3 MAC of halothane, enflurane and isoflurane on cilia beat frequency of human nasal epithelium *in vitro*, Raphael, J. H., *et al.* 116–121

——, Halothane and potassium channels in airway smooth muscle, Fukushima, T., *et al.* 847–853

——, Nitrous oxide or halothane, or both, fail to suppress c-*fos* expression in rat spinal cord dorsal horn neurones after subcutaneous formalin, Sun, W. Z., *et al.* 99–105

——, Pharmacokinetics of rocuronium after bolus and continuous infusion during halothane anaesthesia, McCoy, E. P., *et al.* 29–33

——, Recovery of respiratory ciliary function after depression by inhalation anaesthetic agents: an *in vitro* study using nasal turbinate explants, Raphael, J. H., *et al.* 854–859

——, Sevoflurane–nitrous oxide or halothane–nitrous oxide for paediatric bronchoscopy and gastroscopy, Meretoja, O. A., *et al.* 767–771

——, Time course of potentiation of mivacurium by halothane and isoflurane in children, Meretoja, O. A., *et al.* 235–238

Anaesthetics volatile, halothane , Volatile anaesthetics antagonize nitrous oxide and morphine-induced analgesia in the rat, Goto, T., *et al.* 702–706

Anaesthetics volatile, halothane, Volatile anaesthetics of subanaesthetic isoflurane concentrations evaluated by evoked potentials, Roth, D., *et al.* 38–42

——, Analysis of ethanol in expired air during low-flow isoflurane anaesthesia, Olsson, J., *et al.* 85–89

——, Day-case cataract surgery, Goold, J. E., (*C*) 333

——, Day-case cataract surgery, Maltby, J. R., *et al.*, (*C*) 333

——, Effect of isoflurane and sevoflurane on the magnitude and time course of neuromuscular block produced by vecuronium, pancuronium and atracurium, Vanlinthout, L. E. H., *et al.* 389–395

——, Effect of tramadol on depth of anaesthesia, Coetzee, J. F., *et al.* 415–418

——, Effects of 3 MAC of halothane, enflurane and isoflurane on cilia beat frequency of human nasal epithelium *in vitro*, Raphael, J. H., *et al.* 116–121

——, Effects of propofol and isoflurane on right ventricular function, Boyd, O., *et al.*, (*C*) 598

——, Effects of sevoflurane and isoflurane on systemic vascular

resistance: use of cardiopulmonary bypass as a study model, Rödig, G., *et al.* 9–12
——, Efficiency of a circle system for short surgical cases: comparison of desflurane with isoflurane, Lee, D. J. H., *et al.* 780–782
——, Fuzzy logic control of inspired isoflurane and oxygen concentrations using minimal flow anaesthesia, Curatolo, M., *et al.* 245–250
——, Recovery after desflurane anaesthesia in the infant: comparison with isoflurane, Wolf, A. R., *et al.* 362–364
——, Recovery of respiratory ciliary function after depression by inhalation anaesthetic agents: an *in vitro* study using nasal turbinate explants, Raphael, J. H., *et al.* 854–859
——, Remifentanil reduces auditory and somatosensory evoked responses during isoflurane anaesthesia in a dose-dependent manner, Crabb, I., *et al.* 795–801
——, Sevoflurane, enflurane and isoflurane have no persistent postanaesthetic effects on the central nervous system in cats, Kurata, J., *et al.* 721–725
——, Slow ventilatory dynamics after isocapnic hypoxia and voluntary hyperventilation in humans: effects of isoflurane, Dahan, A., *et al.* 374–381
——, Time course of potentiation of mivacurium by halothane and isoflurane in children, Meretoja, O. A., *et al.* 235–238
——, Volatile anaesthetics antagonize nitrous oxide and morphine-induced analgesia in the rat, Goto, T., *et al.* 702–706
Anaesthetics volatile, sevoflurane, Carbon dioxide output in laparoscopic cholecystectomy, Kazama, T., *et al.* 530–535
——, Effect of isoflurane and sevoflurane on the magnitude and time course of neuromuscular block produced by vecuronium, pancuronium and atracurium, Vanlinthout, L. E. H., *et al.* 389–395
——, Effects of sevoflurane and isoflurane on systemic vascular resistance: use of cardiopulmonary bypass as a study model, Rödig, G., *et al.* 9–12
——, Sevoflurane, enflurane and isoflurane have no persistent postanaesthetic effects on the central nervous system in cats, Kurata, J., *et al.* 721–725
——, Sevoflurane–nitrous oxide or halothane–nitrous oxide for paediatric bronchoscopy and gastroscopy, Meretoja, O. A., *et al.* 767–771
——, Sevoflurane—a long-awaited volatile anaesthetic, Smith, I., *et al.* 435–445
Anaesthetist, risks, Infertility among female hospital doctors in the UK, Maran, N. J., *et al.*, (*ARS*) 581P
——, Occupational x-ray exposure of anaesthetists, McGowan, C., *et al.* 868–869
Anaesthetist, training, A new tracheal tube for difficult intubation, West, M. R. J., *et al.* 673–679
——, Measurement of competence, Goodman, N. W., (*C*) 750
Analgesia, Comparison of caudally administered morphine *vs* hydromorphone in paediatric cardiac surgical patients, Lavoie, J., *et al.*, (*EACTA*) A.70
——, Patient-maintained analgesia with alfentanil after cardiac surgery: a comparison with morphine PCA, Checketts, M. R., *et al.*, (*EACTA*) A.69
Analgesia, obstetric, Extradural analgesia in the first stage of labour, Buggy, D., *et al.*, (*C*) 887
——, Extradural analgesia in the first stage of labour, Fernando, R., *et al.*, (*C*) 886–887
——, Extradural analgesia with clonidine and fentanyl compared with 0.25% bupivacaine in the first stage of labour, Buggy, D. J., *et al.* 319–321
——, Extradural clonidine provides adjunctive pain relief without sedation for women in labour, Tremlett, M. R., *et al.*, (*ARS*) 583–584P
——, Spinal anaesthesia for Caesarean section in women with incomplete extradural analgesia, Stoneham, M., *et al.*, (*C*) 476
Analgesia, paediatric, Comparison of i.v. and s.c. diamorphine infusions for the treatment of acute pain in children, Semple, D., *et al.* 310–312
——, Extradural clonidine for postoperative pain relief, Cook, B., *et al.*, (*C*) 881
——, Extradural clonidine for postoperative pain relief, Nishikawa, T., (*C*) 171
——, Extradural clonidine for postoperative pain relief, Nishikawa, T., (*C*) 881–882
Analgesia, patient-controlled, Dose requirements, efficacy and side effects of morphine and pethidine delivered by patient-controlled analgesia after gynaecological surgery, Stanley, G., *et al.* 484–486
——, Observations on patient-controlled administration of propofol, Thorpe, S. J., *et al.*, (*ARS*) 576P
——, Patient-controlled analgesia and the plasma glucose response to surgery, O'Keefe, V., *et al.*, (*ARS*) 585P
——, Patient-controlled extradural analgesia with bupivacaine, fentanyl, or a mixture of both, after Caesarean section, Cooper, D. W., *et al.* 611–615
——, Patient-controlled propofol: randomized, double-blind dose refinement, Smith, A. F., *et al.*, (*ARS*) 577P
——, Psychological characteristics and patient-controlled analgesia, Thomas, V. J., *et al.*, (*C*) 595
Analgesia, postoperative, Aortic stent surgery, Baranowski, A. P., *et al.*, (*C*) 882–883
——, Aortic stent surgery, Thompson, M. M., *et al.*, (*C*) 883
——, Continuous extradural infusion of ropivacaine for prevention of postoperative pain after major orthopaedic surgery, Turner, G., *et al.* 606–610
——, Dose requirements, efficacy and side effects of morphine and pethidine delivered by patient-controlled analgesia after gynaecological surgery, Stanley, G., *et al.* 484–486
——, Extradural clonidine for postoperative pain relief, Nishikawa, T., (*C*) 171
——, Patient attitudes to perioperative suppository administration for postoperative analgesia, Carroll, M., *et al.*, (*ARS*) 581P
——, Postoperative analgesia by continuous extradural infusion of ropivacaine after upper abdominal surgery, Schug, S. A., *et al.* 487–491
——, Surgical pain is followed not only by spinal sensitization but also by supraspinal antinociception, Wilder-Smith, O. H. G., *et al.* 816–821
Analgesia, pre-emptive, Absence of an early pre-emptive effect after thoracic extradural bupivacaine in thoracic surgery, Aguilar, J. L., *et al.* 72–76
——, Does pre-incisional thoracic extradural block combined with diclofenac reduce postoperative pain after abdominal hysterectomy? Espinet, A., *et al.* 209–213
——, Influence of dose and timing of administration of morphine on postoperative pain and analgesic requirements, Mansfield, M. D., *et al.* 358–361
——, Nitrous oxide or halothane, or both, fail to suppress c-*fos* expression in rat spinal cord dorsal horn neurones after subcutaneous formalin, Sun, W. Z., *et al.* 99–105
——, Remembrance of times past: the significance of c-*fos* in pain, Munglani, R., *et al.*, (*E*) 1–4
——, Surgical pain is followed not only by spinal sensitization but also by supraspinal antinociception, Wilder-Smith, O. H. G., *et al.* 816–821
Analgesic techniques, caudal, Extradural clonidine for postoperative pain relief, Nishikawa, T., (*C*) 171
Analgesic techniques, extradural, Absence of an early pre-emptive effect after thoracic extradural bupivacaine in thoracic surgery, Aguilar, J. L., *et al.* 72–76
——, Extradural clonidine for postoperative pain relief, Cook, B., *et al.*, (*C*) 881
——, Extradural clonidine for postoperative pain relief, Nishikawa, T., (*C*) 881–882
Analgesic techniques, infusion, Pulmonary uptake of sufentanil during and after constant rate infusion, Boer, F., *et al.* 203–208
Analgesic techniques, i.v., Comparison of i.v. and s.c. diamorphine infusions for the treatment of acute pain in children, Semple, D., *et al.* 310–312
Analgesic techniques, regional, Use of regional i.v. morphine analgesia in patients undergoing total knee arthroplasty, Corbett, A. R., *et al.*, (*ARS*) 593–594P
Analgesic techniques, subcutaneous, Comparison of i.v. and s.c. diamorphine infusions for the treatment of acute pain in children, Semple, D., *et al.* 310–312
Analgesics non-opioid, aspirin, Effect of aspirin in single first coronary artery bypass grafting, Vuylsteke, A., *et al.*, (*EACTA*) A.51
Analgesics non-opioid, diclofenac, Morphine consumption in patients receiving rectal paracetamol and diclofenac alone and in combination, Montgomery, J. E., *et al.*, (*ARS*) 591–592P
——, Patient attitudes to perioperative suppository administration for postoperative analgesia, Carroll, M., *et al.*, (*ARS*) 581P
Analgesics non-opioid, ketorolac, Is tramadol better than ketorolac after day-case laparoscopy? Sabar, M. A., *et al.*, (*ARS*) 584P
Analgesics non-opioid, naproxen, Naproxen after day-case laparoscopic sterilization, Dunn, T. J., *et al.*, (*C*) 168
——, Naproxen after day-case laparoscopic sterilization, Williams, P. I., (*C*) 168
Analgesics non-opioid, paracetamol, Morphine consumption in patients receiving rectal paracetamol and diclofenac alone and in combination, Montgomery, J. E., *et al.*, (*ARS*) 591–592P
Analgesics opioid, Inadvertent infusion of glucose saline into the extradural space, Mphanza, T., (*C*) 332

Analgesics opioid, alfentanil, Effect of the addition of alfentanil to lignocaine during axillary brachial plexus anaesthesia, Gormley, W. P., *et al.* 802–805

——, Patient-maintained analgesia with alfentanil after cardiac surgery: a comparison with morphine PCA, Checketts, M. R., *et al.*, (*EACTA*) A.69

Analgesics opioid, diamorphine, Comparison of i.v. and s.c. diamorphine infusions for the treatment of acute pain in children, Semple, D., *et al.* 310–312

Analgesics opioid, fentanyl, Antinociceptive actions of intrathecal xylazine: interactions with spinal cord opioid pathways, Goodchild, C. S., *et al.* 544–551

——, Extradural analgesia in the first stage of labour, Buggy, D., *et al.*, (*C*) 887

——, Extradural analgesia in the first stage of labour, Fernando, R., *et al.*, (*C*) 886–887

——, Extradural analgesia with clonidine and fentanyl compared with 0.25% bupivacaine in the first stage of labour, Buggy, D. J., *et al.* 319–321

——, Fentanyl increases intracellular Ca^{2+} concentrations in SH-SY5Y cells, Wandless, A. L., *et al.* 461–463

——, Patient-controlled extradural analgesia with bupivacaine, fentanyl, or a mixture of both, after Caesarean section, Cooper, D. W., *et al.* 611–615

Analgesics opioid, hydromorphone, Comparison of caudally administered morphine *vs* hydromorphone in paediatric cardiac surgical patients, Lavoie, J., *et al.*, (*EACTA*) A.70

Analgesics opioid, morphine, Comparison of caudally administered morphine *vs* hydromorphone in paediatric cardiac surgical patients, Lavoie, J., *et al.*, (*EACTA*) A.70

——, Dose requirements, efficacy and side effects of morphine and pethidine delivered by patient-controlled analgesia after gynaecological surgery, Stanley, G., *et al.* 484–486

——, Effects of morphine on atrial preparations obtained from non-failing and failing human hearts, Llobel, F., *et al.* 106–110

——, Effects of morphine on human nasal cilia beat frequency *in vitro*, Selwyn, D. A., *et al.* 274–277

——, Immunoglobulin and interleukin 2 production *ex vivo/in vitro* during treatment with oral retarded morphine, Palm, S., *et al.*, (*ARS*) 588–589P

——, Influence of dose and timing of administration of morphine on postoperative pain and analgesic requirements, Mansfield, M. D., *et al.* 358–361

——, Morphine consumption in patients receiving rectal paracetamol and diclofenac alone and in combination, Montgomery, J. E., *et al.*, (*ARS*) 591–592P

——, Patient-maintained analgesia with alfentanil after cardiac surgery: a comparison with morphine PCA, Checketts, M. R., *et al.*, (*EACTA*) A.69

——, Spinal clonidine produces less urinary retention than spinal morphine, Gentili, M., *et al.* 872–873

——, Use of regional i.v. morphine analgesia in patients undergoing total knee arthroplasty, Corbett, A. R., *et al.*, (*ARS*) 593–594P

——, Ventilatory response to carbon dioxide, Dahan, A., *et al.*, (*C*) 747

——, Ventilatory response to carbon dioxide, Saito, Y., *et al.*, (*C*) 747–748

——, Volatile anaesthetics antagonize nitrous oxide and morphine-induced analgesia in the rat, Goto, T., *et al.* 702–706

Analgesics opioid, pethidine, Dose requirements, efficacy and side effects of morphine and pethidine delivered by patient-controlled analgesia after gynaecological surgery, Stanley, G., *et al.* 484–486

Analgesics opioid, remifentanil, Remifentanil by infusion achieves predictable blood concentrations, Poulton, B. B., *et al.*, (*EACTA*) A.15

——, Remifentanil reduces auditory and somatosensory evoked responses during isoflurane anaesthesia in a dose-dependent manner, Crabb, I., *et al.* 795–801

——, Remifentanil—an opioid for the 21st century, Thompson, J. P., *et al.*, (*E*) 341–343

Analgesics opioid, sufentanil, Pulmonary uptake of sufentanil during and after constant rate infusion, Boer, F., *et al.* 203–208

Analgesics opioid, tramadol, Effect of tramadol on depth of anaesthesia, Coetzee, J. F., *et al.* 415–418

——, Is tramadol better than ketorolac after day-case laparoscopy? Sabar, M. A., *et al.*, (*ARS*) 584P

Anatomy, spinal column, Anatomical configuration of the spinal column in the supine position. III. Comparison of adolescent and adult volunteers, Hirabayashi, Y., *et al.* 508–510

Anesthesia and Intensive Care for Patients with Liver Disease, Park, G. R., *et al.*, (editors), (*R*) 338

Anesthesiology, House Officer Series, Berry, A. J., *et al.*, (editors), (*R*) 891

Antacids, omeprazole, Comparison of the effect of two dose schedules of oral omeprazole with oral ranitidine on gastric aspirate pH and volume in patients undergoing elective surgery, Levack, I. D., *et al.* 567–569

Antacids, ranitidine, Comparison of the effect of two dose schedules of oral omeprazole with oral ranitidine on gastric aspirate pH and volume in patients undergoing elective surgery, Levack, I. D., *et al.* 567–569

Antagonists benzodiazepine, flumazenil, Periodic cardiovascular and ventilatory activity during midazolam sedation, Galletly, D. C., *et al.* 503–507

Antagonists neuromuscular block, edrophonium, Edrophonium antagonism of intense mivacurium-induced neuromuscular block in children, Abdulatif, M., *et al.* 239–244

Antagonists neuromuscular block, neostigmine, Change in neostigmine ampoules, Mackersie, A. M., (*C*) 334

Antagonists serotonin, tropisetron, Single dose i.v. tropisetron in the prevention of postoperative nausea and vomiting after gynaecological surgery, Capouet, V., *et al.* 54–60

Antibiotics, Management of pre-eclampsia, Mushambi, M. C., *et al.*, (*C*) 889–890

——, Management of pre-eclampsia, Ward, J. E. H., *et al.*, (*C*) 889

Arterial pressure, Haemodynamic effects of continued sedation during tracheal extubation, Conti, J., *et al.*, (*EACTA*) A.72

Arterial pressure, Radial artery tonometry: moderately accurate but unpredictable technique of continuous non-invasive arterial pressure measurement, Weiss, B. M., *et al.* 405–411

Arterial pressure, drug effects, Periodic cardiovascular and ventilatory activity during midazolam sedation, Galletly, D. C., *et al.* 503–507

Arterial pressure, hypertension, Management of pre-eclampsia, Mushambi, M. C., *et al.*, (*C*) 889–890

——, Management of pre-eclampsia, Ward, J. E. H., *et al.*, (*C*) 889

——, Recent developments in the pathophysiology and management of pre-eclampsia, Mushambi, M. C., *et al.* 133–148

Arterial pressure, hypotension, Volume preloading, spinal anaesthesia and Caesarean section, Lawes, E. G., (*C*) 334–335

——, Volume preloading, spinal anaesthesia and Caesarean section, Mallick, A., *et al.*, (*C*) 335

——, Volume preloading, spinal anaesthesia and Caesarean section, Reid, J., *et al.*, (*C*) 335–336

Arterial pressure, measurement, Radial artery tonometry: moderately accurate but unpredictable technique of continuous non-invasive arterial pressure measurement, Weiss, B. M., *et al.* 405–411

Arteries, Effects of propofol on rabbit mesenteric arteries and veins, Kamitani, K., (*C*) 333–334

——, Effects of propofol on rabbit mesenteric arteries and veins, Stratford, N., (*C*) 333

——, Methylprednisolone inhibits endotoxin-induced depression of contractile function in human arteries *in vitro*, Tsuneyoshi, I., *et al.* 251–257

Arteries, aorta, Aortic stent surgery, Baranowski, A. P., *et al.*, (*C*) 882–883

——, Aortic stent surgery, Thompson, M. M., *et al.*, (*C*) 883

Arteries, mammary artery, Use of internal mammary artery improves prognosis in patients under 70 undergoing combined valve and coronary artery surgery, Herijgers, P., *et al.*, (*EACTA*) A.79

Arteries, radial, Topical nitroglycerin dilates the radial artery, Gota, M., *et al.*, (*EACTA*) A.20

Arteries, relaxation, Effect of phosphodiesterase inhibitors on human arteries *in vitro*, Vroom, M. B., *et al.* 122–129

Ataractics, cannabis, Cannabis as a medicine, West, M. E., *et al.*, (*C*) 167

Baillière's Clinical Anaesthesiology: New Pharmacological Vistas, Fink, E. J. jr, *et al.*, (editors), (*R*) 173

Basics of Transoesophageal Echocardiography, Rafferty, T. D., (editor), (*R*) 173

Beta blockers, Comparison of sotalol and digoxin in the prevention of early supraventricular arrhythmias after coronary artery bypass graft (CABG), Jadoul, J. L., *et al.*, (*EACTA*) A.67

——, Effect of β-blockers *versus* calcium channel blockers in myocardial revascularization without cardiopulmonary bypass in pigs, Rajek, A., *et al.*, (*EACTA*) A.39

Blood, haemodilution, Haemodynamic effects of moderate normovolaemic haemodilution in conscious and anaesthetized patients, Biboulet, P., *et al.* 81–84

Biocompatibility, Comparative assessment of the biocompatibility of 4 types of tubing for cardiopulmonary bypass, Briquet, F., *et al.*, (*EACTA*) A.31

Blood, anaemia, Anaemia and transfusion; major determinants of pressure sores after cardiac surgery, Baele, Ph., *et al.*, (*EACTA*) A.60

Blood, anticoagulants, heparin, Venous thromboembolism and cardiovascular surgery, Bullingham, A., *et al.*, (*C*) 473

——, Venous thromboembolism and cardiovascular surgery, McDonald, D. S., (*C*) 473

Blood, antifibrinolytics, High dose aprotinin *vs* tranexamic acid in elective cardiac surgery: effects on bleeding and necessity of transfusion, Casati, V., *et al.*, (*EACTA*) A.53

——, Plasma levels of tranexamic acid after two injections during cardiac surgery with cardiopulmonary bypass, Isetta, C., *et al.*, (*EACTA*) A.52

——, Very low dose aprotinin in cardiac surgery, Pétrie, J., *et al.*, (*EACTA*) A.54

Blood, autotransfusion, Autologous blood processing during cardiac surgery: haemofiltration *versus* cell washing, Walpoth, B. H., *et al.*, (*EACTA*) A.58

——, Autotransfusion of unwashed shed blood after CABG, using the Atrium 2052® blood recovery system, Gouwy, S., *et al.*, (*EACTA*) A.59

Blood, coagulation, Autotransfusion of unwashed shed blood after CABG, using the Atrium 2052® blood recovery system, Gouwy, S., *et al.*, (*EACTA*) A.59

——, Effect of aspirin in single first coronary artery bypass grafting, Vuylsteke, A., *et al.*, (*EACTA*) A.51

——, Haemodilution induces a hypercoagulable state, Ruttmann, T. G., *et al.* 412–414

——, Haemostatic changes caused by i.v. regional anaesthesia with lignocaine, Niemi, T. T., *et al.* 822–828

——, High dose aprotinin *vs* tranexamic acid in elective cardiac surgery: effects on bleeding and necessity of transfusion, Casati, V., *et al.*, (*EACTA*) A.53

——, Plasma levels of tranexamic acid after two injections during cardiac surgery with cardiopulmonary bypass, Isetta, C., *et al.*, (*EACTA*) A.52

——, Very low dose aprotinin in cardiac surgery, Pétrie, J., *et al.*, (*EACTA*) A.54

Blood, colloid oncotic pressure, Cardiopulmonary bypass with modified fluid gelatin and heparin-coated circuits, Jansen, P. G. M., *et al.* 13–19

Blood, conservation, Autologous blood processing during cardiac surgery: haemofiltration *versus* cell washing, Walpoth, B. H., *et al.*, (*EACTA*) A.58

——, Pilot evaluation of RMI haemoconcentrator during cardiopulmonary bypass, Dhond, G., *et al.*, (*EACTA*) A.57

Blood, erythrocytes, Effect of propofol and thiopentone on free radical mediated oxidative stress of the erythrocyte, Murphy, P. G., *et al.* 536–543

Blood, erythropoietin, Use of recombinant human erythropoietin to facilitate liver transplantation in a Jehovah's Witness, Snook, N. J., *et al.* 740–743

Blood, flow, A new method for cerebral blood flow measurement, Mielck, F., *et al.*, (*EACTA*) A.12

——, Effects of dopamine and dopexamine on splanchnic microcirculation during major surgery in humans, Bellamy, M. C., *et al.*, (*ARS*) 587P

——, Experimental evaluation of a single breath inert gas technique for measurement of myocardial blood flow, Kazmaier, S., *et al.*, (*EACTA*) A.5

——, Quality control of coronary bypass surgery: intraoperative transit time flow measurement, Walpoth, B. H., *et al.*, (*EACTA*) A.7

——, Splanchnic blood flow during cardiopulmonary bypass assessed by indicator dilution technique, Gårdebäck, M., *et al.*, (*EACTA*) A.36

——, The effects of propofol on cerebral blood flow velocity and oxygenation during cardiopulmonary bypass, Ederberg, S., *et al.*, (*EACTA*) A.17

Blood, flow, feto-uteroplacental, Maternal and uteroplacental haemodynamic state in pre-eclamptic patients during spinal anaesthesia for Caesarean section, Karinen, J., *et al.* 616–620

Blood, flow, mucosal, Effect of low-dose dopamine on intestinal villus microcirculation during normotensive endotoxaemia in rats, Schmidt, H., *et al.* 707–712

Blood, flow, splanchnic, Effects of desflurane and isoflurane on splanchnic microcirculation during surgery, O'Beirne, H., *et al.*, (*ARS*) 592P

Blood, glucose, Patient-controlled analgesia and the plasma glucose response to surgery, O'Keefe, V., *et al.*, (*ARS*) 585P

——, Rheological properties of commonly used plasma substitutes during preoperative normovolaemic acute haemodilution, Freyburger, G., *et al.* 519–525

Blood, haemofiltration, Autologous blood processing during cardiac surgery: haemofiltration *versus* cell washing, Walpoth, B. H., *et al.*, (*EACTA*) A.58

Blood, haemoglobin, Continuous temperature and O_2 saturation monitoring of jugular blood during DHCA procedures for aortic surgery, Paino, R., *et al.*, (*EACTA*) A.40

——, Does Parsonnet score predict the usefulness of Sv_{O_2} pulmonary artery catheter (Sv_{O_2}PAC) during heart surgery? Vedrinne, C., *et al.*, (*EACTA*) A.85

——, Effect of propofol and thiopentone on free radical mediated oxidative stress of the erythrocyte, Murphy, P. G., *et al.* 536–543

——, Kinetics of methaemoglobin and serum nitrogen oxide production during inhalation of nitric oxide in volunteers, Young, J. D., *et al.* 652–656

Blood, haemolysis, Effect of propofol and thiopentone on free radical mediated oxidative stress of the erythrocyte, Murphy, P. G., *et al.* 536–543

Blood, haemostasis, Haemostatic changes caused by i.v. regional anaesthesia with lignocaine, Niemi, T. T., *et al.* 822–828

Blood, monocytes, Does propofol change the phenotype of monocytes in thoracic surgery? Laßnigg, A., *et al.*, (*EACTA*) A.18

Blood, neutrophils, Flow cytometry evaluation of the *in vitro* effects of four i.v. anaesthetics on the respiratory burst of human neutrophils, Leuwer, M., *et al.*, (*ARS*) 585P

Blood, products, Use of blood products in cardiovascular surgery 4 years after the Sanguis study, Deneys, V., *et al.*, (*EACTA*) A.56

Blood, replacement, Consensus statement on autologous transfusion, Royal College of Physicians of Edinburgh, 470

——, Rheological properties of commonly used plasma substitutes during preoperative normovolaemic acute haemodilution, Freyburger, G., *et al.* 519–525

Blood, substitutes, Rheological properties of commonly used plasma substitutes during preoperative normovolaemic acute haemodilution, Freyburger, G., *et al.* 519–525

Blood, transfusion, Consensus statement on autologous transfusion, Royal College of Physicians of Edinburgh, 470

Blood, volume, Effects and interactions of myocardial ischaemia and alterations in circulating blood volume on canine left ventricular diastolic function, Dalmas, S., *et al.* 419–427

Book Reviews

- *A Physicians's Guide to the Internet*, Hancock, L., (*R*) 893
- *A Practical Approach to Cardiac Anesthesia*, Hensley, F. A. jr, *et al.*, (editors), (*R*) 174
- *Acute Pain Management: A Practical Guide*, Macintyre, P. E., *et al.*, (*R*) 892
- *Anaesthesia and Critical Care Manual*, 2nd Edn, Cunningham, A. J., (editor), (*R*) 338
- *Anaesthesia for Surgery of the Spine*, Porter, S. S., (editor), (*R*) 892
- *Anaesthesia: Review 11*, Kaufman, L., *et al.*, (editors), (*R*) 174
- *Anesthesia and Intensive Care for Patients with Liver Disease*, Park, G. R., *et al.*, (editors), (*R*) 338
- *Anesthesiology, House Officer Series*, Berry, A. J., *et al.*, (editors), (*R*) 891
- *Baillière's Clinical Anaesthesiology: New Pharmacological Vistas*, Fink, E. J. jr, *et al.*, (editors), (*R*) 173
- *Basics of Transoesophageal Echocardiography*, Rafferty, T. D., (editor), (*R*) 173
- *Difficult Hypertension: Practical Management and Decision Making*, Kendall, M. J., *et al.*, (editors), (*R*) 891–892
- *Essentials of Anaesthetic Equipment*, Al-Shaikh, B., *et al.*, (*R*) 751
- *Handbook of Neonatal Anaesthesia*, Hughes, D. G., *et al.*, (editors), (*R*) 599
- *Intensive Care: A Concise Textbook*, 2nd Edn, Hind, C. J., *et al.*, (*R*) 599
- *600 MCQs in Anaesthesia: Clinical Practice*, 2nd Edn, Goodman, N. W., *et al.*, (*R*) 751
- *Modulation of the Inflammatory Response in Severe Sepsis*, Tellado, J. M., *et al.*, (editors), (*R*) 173–174
- *Neuro-anaesthetic Practice*, Van Aken, H., (editor), (*R*) 599
- *Neuromuscular Block*, Feldman, S., (*R*) 893

Book Reviews
Ophthalmic Anaesthesia—A Practical Handbook, 2nd Edn, Smith, G. B., *et al.*, (*R*) 891
Primer of Intraoperative Neurophysiologic Monitoring, Russell, G. B., *et al.*, (editors), (*R*) 477
Principles and Practice Series: Respiratory Support, Sykes, K., (*R*) 338
Regional Anesthesia: An Atlas of Anatomy and Techniques, Hahn, M. B., *et al.*, (editors), (*R*) 751
Sedation and Analgesia in the Critically Ill, Park, G. R., *et al.*, (editors), (*R*) 174
The ABC of Resuscitation, 3rd Edn, Colquhoun, M. C., *et al.*, (editors), (*R*) 338–339
Understanding Anaesthesia, 3rd Edn, Carrie, L. E. S., *et al.*, (*R*) 892–893
Wylie & Churchill-Davidson's A Practice of Anaesthesia, 6th Edn. Healy, T. E. J., *et al.*, (editors), (*R*) 477
Brain, Continuous temperature and O_2 saturation monitoring of jugular blood during DHCA procedures for aortic surgery, Paino, R., *et al.*, (*EACTA*) A.40
——, The effects of propofol on cerebral blood flow velocity and oxygenation during cardiopulmonary bypass, Ederberg, S., *et al.*, (*EACTA*) A.17
Brain, blood flow, Cerebral blood flow response to changes in CO_2 at hypothermia and normothermia. A controlled, randomized crossover study, Weyland, A., *et al.*, (*EACTA*) A.35
——, Sepsis-induced vasoparalysis does not involve the cerebral vasculature: indirect evidence from autoregulation and carbon dioxide reactivity studies, Matta, B. F., *et al.* 790–794
——, Use of near infrared spectroscopy to estimate cerebral blood flow in conscious and anaesthetized adult subjects, Owen-Reece, H., *et al.* 43–48
Brain, carbon dioxide reactivity, Sepsis-induced vasoparalysis does not involve the cerebral vasculature: indirect evidence from autoregulation and carbon dioxide reactivity studies, Matta, B. F., *et al.* 790–794
Brain, cerebral cortex, Is the dihydropyridine binding site on neuronal L-type calcium channels a target for i.v. anaesthetic agents? Hirota, K., *et al.*, (*ARS*) 591P
Brain, damage, Epiaortic scanning of the ascending aorta identifies arteriosclerotic plaques and changes surgical practice during CABG? van der Linden, J., *et al.*, (*EACTA*) A.82
Brain, electroencephalography, Auditory evoked responses, median frequency and 95% spectral edge during anaesthesia with desflurane and nitrous oxide, Pal, S. K., *et al.*, (*ARS*) 577P
——, Evaluation of bispectral index as an objective sedation score in the intensive care unit, Pearson, A. J., *et al.*, (*ARS*) 577–578P
——, Sevoflurane, enflurane and isoflurane have no persistent postanaesthetic effects on the central nervous system in cats, Kurata, J., *et al.* 721–725
Brain, evoked potentials, Auditory evoked responses, median frequency and 95% spectral edge during anaesthesia with desflurane and nitrous oxide, Pal, S. K., *et al.*, (*ARS*) 577P
——, Effect of suxamethonium on the auditory evoked response in humans, Brunner, M. D., *et al.* 34–37
——, Remifentanil reduces auditory and somatosensory evoked responses during isoflurane anaesthesia in a dose-dependent manner, Crabb, I., *et al.* 795–801
——, Suxamethonium and auditory evoked potentials, Brunner, M. D., *et al.*, (*C*) 881
——, Suxamethonium and auditory evoked potentials, Ponte, J., (*C*) 881
Brain, injury, Validation of the Edslab dual lumen oximetry catheter for continuous monitoring of jugular bulb oxygen saturation after severe head injury, Souter, M. J., *et al.* 744–746
Brain, ischaemia, Validation of the Edslab dual lumen oximetry catheter for continuous monitoring of jugular bulb oxygen saturation after severe head injury, Souter, M. J., *et al.* 744–746
Burns, Analgesic and anti-inflammatory effects of lignocaine–prilocaine (EMLA) cream in human burn injury, Pedersen, J. L., *et al.* 806–810
——, Effect of systemic *N*-methyl-D-aspartate receptor antagonist (ketamine) on primary and secondary hyperalgesia in humans, Ilkjaer, S., *et al.* 829–834

Calcium antagonists, Effect of β-blockers *versus* calcium channel blockers in myocardial revascularization without cardiopulmonary bypass in pigs, Rajek, A., *et al.*, (*EACTA*) A.39
——, Pharmacokinetics and haemodynamic effects of an ultrashort-acting calcium antagonist, Nordlander, M., *et al.*, (*EACTA*) A.24
Calcium channel block, diltiazem, Comparison of nicardipine, diltiazem and verapamil for controlling the cardiovascular responses to tracheal intubation, Mikawa, K., *et al.* 221–226
Calcium channel block, nicardipine, Comparison of nicardipine, diltiazem and verapamil for controlling the cardiovascular responses to tracheal intubation, Mikawa, K., *et al.* 221–226
Calcium channel block, verapamil, Comparison of nicardipine, diltiazem and verapamil for controlling the cardiovascular responses to tracheal intubation, Mikawa, K., *et al.* 221–226
Calcium sensitizer, levosimendan, Levosimendan is a more potent inotropic agent than amrinone after ischaemia in isolated perfused guinea pig hearts, Süzer, Ö., *et al.*, (*EACTA*) A.9
——, The effect of the calcium sensitizer levosimendan on normal and stunned left ventricular myocardium, Weterings, C. J., *et al.*, (*EACTA*) A.8
Carbon dioxide, embolism, Effects of carbon dioxide embolism with nitrous oxide in the inspired gas in piglets, Nyarwaya, J.-B., *et al.* 428–434
Cardiac surgery, Anaemia and transfusion; major determinants of pressure sores after cardiac surgery, Baele, Ph., *et al.*, (*EACTA*) A.60
——, Aprotinin treatment does not impair renal function during and after cardiac surgery, Schweizer, A., *et al.*, (*EACTA*) A.55
——, Arrhythmias after valvular surgery: a randomized double-blind Holter comparative trial of St Thomas' (*ST*) *vs* CPS cardioplegia, Vedrinne, C., *et al.*, (*EACTA*) A.66
——, Autologous blood processing during cardiac surgery: haemofiltration *versus* cell washing, Walpoth, B. H., *et al.*, (*EACTA*) A.58
——, Autotransfusion of unwashed shed blood after CABG, using the Atrium 2052® blood recovery system, Gouwy, S., *et al.*, (*EACTA*) A.59
——, Cardiac surgical practices in the United States of America and Europe: striking similarities and minor differences, Vuylsteke, A., *et al.*, (*EACTA*) A.77
——, Changes of mitral inflow patterns as assessed by transoesophageal echocardiography following cardiac surgery: are they of clinical significance? Schmidlin, D., *et al.*, (*EACTA*) A.48
——, Comparison of caudally administered morphine *vs* hydromorphone in paediatric cardiac surgical patients, Lavoie, J., *et al.*, (*EACTA*) A.70
——, Comparison of sotalol and digoxin in the prevention of early supraventricular arrhythmias after coronary artery bypass graft (CABG), Jadoul, J. L., *et al.*, (*EACTA*) A.67
——, Correlation of predicted and recorded concentrations of nitric oxide during long-term inhalation in infants after cardiac surgery, Knapik, P., *et al.*, (*EACTA*) A.28
——, Does Parsonnet score predict the usefulness of Sv_{O_2} pulmonary artery catheter (Sv_{O_2}PAC) during heart surgery? Vedrinne, C., *et al.*, (*EACTA*) A.85
——, Does perioperative transoesophageal echocardiography change the therapy of cardiothoracic patients? Brase, R., *et al.*, (*EACTA*) A.47
——, Double blind, placebo controlled study of the effects of remacemide HCl on neuropsychological deficits following coronary artery surgery, Arowsmith, J. E., *et al.*, (*EACTA*) A.83
——, Effect of aspirin in single first coronary artery bypass grafting, Vuylsteke, A., *et al.*, (*EACTA*) A.51
——, Effects of lidoflazine on left ventricular function, Dhirue, G. L., *et al.*, (*EACTA*) A.10
——, Free fatty acid (FFA) uptake immediately after routine coronary artery bypass surgery (CABG), Pietersen, H. G., *et al.*, (*EACTA*) A.2
——, Haemodynamic effects of continued sedation during tracheal extubation, Conti, J., *et al.*, (*EACTA*) A.72
——, Heparin-coated circuits reduce postoperative lung complications in high-risk cardiac patients, Ranucci, M., *et al.*, (*EACTA*) A.71
——, High dose aprotinin *vs* tranexamic acid in elective cardiac surgery: effects on bleeding and necessity of transfusion, Casati, V., *et al.*, (*EACTA*) A.53
——, Myocardial ischaemia and heart rate variability after coronary bypass surgery, Kentala, E., *et al.*, (*EACTA*) A.64
——, Nausea and vomiting after cardiac surgery, Grebenik, C., *et al.*, (*EACTA*) A.76
——, Non-invasive pressure support ventilation (NPSV) as an alternative to reintubation, Paulus, S., *et al.*, (*EACTA*) A.73
——, Organ dysfunctions after cardiac surgery: definitions and prognosis, Calvert, B., *et al.*, (*EACTA*) A.78

——, Oxygen consumption during early mobilization after CABG surgery in patients with normal cardiac function, Kirkeby-Garstad, I., *et al.*, (*EACTA*) A.74
——, Patient-maintained analgesia with alfentanil after cardiac surgery: a comparison with morphine PCA, Checketts, M. R., *et al.*, (*EACTA*) A.69
——, Perioperative myocardial infarction (PMI) in cardiac surgery—risk factors and clinical outcome, Svedjeholm, P., *et al.*, (*EACTA*) A.61
——, Phospholipase A_2 in cardiac surgery, Håkanson, E., *et al.*, (*EACTA*) A.1
——, Pilot evaluation of RMI haemoconcentrator during cardiopulmonary bypass, Dhond, G., *et al.*, (*EACTA*) A.57
——, Plasma levels of tranexamic acid after two injections during cardiac surgery with cardiopulmonary bypass, Isetta, C., *et al.*, (*EACTA*) A.52
——, QTc-dispersion in patients undergoing CABG surgery, Fruhwald, S., *et al.*, (*EACTA*) A.65
——, Scoring systems *versus* subjective assessment as an outcome predictor in adult cardiac surgery, Smith, E., *et al.*, (*EACTA*) A.86
——, Time course of serial serum troponin I levels after coronary artery bypass surgery (CABG), Filley, S., *et al.*, (*EACTA*) A.63
——, Transoesophageal echocardiography and intraoperative evaluation of left ventricular performance, Jovic, M., *et al.*, (*EACTA*) A.49
——, Troponin-T for asessment of myocardial damage in CABG surgery, Dahlin, L. G., *et al.*, (*EACTA*) A.62
——, Type of perioperative antihypertensive treatment delays extubation and prolongs ICU stay in cardiac surgery, Vuylsteke, A., *et al.*, (*EACTA*) A.30
——, Use of blood products in cardiovascular surgery 4 years after the Sanguis study, Deneys, V., *et al.*, (*EACTA*) A.56
——, Use of internal mammary artery improves prognosis in patients under 70 undergoing combined valve and coronary artery surgery, Herijgers, P., *et al.*, (*EACTA*) A.79
——, Very low dose aprotinin in cardiac surgery, Pétrie, J., *et al.*, (*EACTA*) A.54
Cardiopulmonary bypass, A comparison of core temperature with thermal energy balance in predicting adequacy of rewarming from hypothermic cardiopulmonary bypass, Deakin, C. D., *et al.*, (*EACTA*) A.41
——, Blood lactate during cardiopulmonary bypass with a lactated priming solution, Hett, D., *et al.*, (*EACTA*) A.33
——, Cerebral blood flow response to changes in CO_2 at hypothermia and normothermia. A controlled, randomized crossover study, Weyland, A., *et al.*, (*EACTA*) A.35
——, Comparative assessment of the biocompatibility of 4 types of tubing for cardiopulmonary bypass, Briquet, F., *et al.*, (*EACTA*) A.31
——, Continuous temperature and O_2 saturation monitoring of jugular blood during DHCA procedures for aortic surgery, Paino, R., *et al.*, (*EACTA*) A.40
——, Convective warming overcomes effects of cooling after cardiopulmonary bypass, Knowles, P. R., *et al.*, (*EACTA*) A.42
——, Effect of β-blockers *versus* calcium channel blockers in myocardial revascularization without cardiopulmonary bypass in pigs, Rajek, A., *et al.*, (*EACTA*) A.39
——, Perioperative changes in receptors for ICAM-1/CD54 and immunglobulin G on monocytes by extracorporeal circulation (ECC), Hiesmayr, M., *et al.*, (*EACTA*) A.32
——, Splanchnic blood flow during cardiopulmonary bypass assessed by indicator dilution technique, Gårdebäck, M., *et al.*, (*EACTA*) A.36
——, Standard pump flow rate and Sv_{O_2} above 60% do not imply adequate oxygen delivery during CPB, Ryckwaert, F., *et al.*, (*EACTA*) A.34
Cardiovascular system, effects, Aprotinin during liver transplantation, Cottam, S., *et al.*, (*C*) 882
——, Aprotinin during liver transplantation, Lentschener, C., *et al.*, (*C*) 882
——, Comparison of nicardipine, diltiazem and verapamil for controlling the cardiovascular responses to tracheal intubation, Mikawa, K., *et al.* 221–226
——, Comparison of the effects of urapidil and sodium nitroprusside on haemodynamic state, myocardial metabolism and function in patients during coronary artery surgery, van der Stroom, J. G., *et al.* 645–651
——, Effects of sevoflurane and isoflurane on systemic vascular resistance: use of cardiopulmonary bypass as a study model, Rödig, G., *et al.* 9–12
——, Haemodynamic effects of moderate normovolaemic haemodilution in conscious and anaesthetized patients, Biboulet, P., *et al.* 81–84
——, Haemodynamic responses to incision and sternotomy in relation to the auditory evoked potential and spontaneous EEG, de Beer, N. A. M., *et al.* 685–693
——, Laparoscopic cholecystectomy: haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position, O'Leary, E., *et al.* 640–644
Central nervous system, A new method for cerebral blood flow measurement, Mielck, F., *et al.*, (*EACTA*) A.12
——, Double blind, placebo controlled study of the effects of remacemide HCl on neuropsychological deficits following coronary artery surgery, Arowsmith, J. E., *et al.*, (*EACTA*) A.83
——, Epiaortic scanning of the ascending aorta identifies arteriosclerotic plaques and changes surgical practice during CABG? van der Linden, J., *et al.*, (*EACTA*) A.82
Central nervous system, damage, Brain death induced haemodynamic failure in the rat is solely due to autonomic denervation, Herijgers, P., *et al.*, (*EACTA*) A.13
——, Serotonin induces coronary spasms after brain death in dogs, Herijgers, P., *et al.*, (*EACTA*) A.14
Cerebrospinal fluid, Reducing the potential morbidity of an unintentional spinal anaesthetic by aspirating cerebrospinal fluid, Southorn, P., *et al.* 467–469
Children, Dose of propofol for laryngeal mask airway insertion in children: effect of premedication with midazolam, Martlew, R. A., *et al.* 308–309
——, Edrophonium antagonism of intense mivacurium-induced neuromuscular block in children, Abdulatif, M., *et al.* 239–244
——, Midazolam *vs* trimeprazine premedication for children during day-care surgery, Nathwani, D., *et al.*, (*ARS*) 589P
——, Parental or anaesthetist's ability to predict a 'stormy' induction in young children, Lyons, B., *et al.*, (*ARS*) 589P
——, Removal of the laryngeal mask airway in children: anaesthetized compared with awake, Kitching, A. J., *et al.* 874–876
——, Sevoflurane–nitrous oxide or halothane–nitrous oxide for paediatric bronchoscopy and gastroscopy, Meretoja, O. A., *et al.* 767–771
——, Smaller children have greater bupivacaine plasma concentrations after ilioinguinal block, Smith, T., *et al.* 452–455
——, Suxamethonium in children, Farrell, P. T., (*C*) 883–884
——, Suxamethonium in children, Fiacchino, F., *et al.*, (*C*) 883
——, Suxamethonium in children, Hopkins, P. M., (*C*) 884
Complications, A multifactorial analysis to explain inadequate surgical analgesia after extradural block, Curatolo, M., *et al.*, (*e*) 598
——, Anaemia and transfusion; major determinants of pressure sores after cardiac surgery, Baele, Ph., *et al.*, (*EACTA*) A.60
——, Double blind, placebo controlled study of the effects of remacemide HCl on neuropsychological deficits following coronary artery surgery, Arowsmith, J. E., *et al.*, (*EACTA*) A.83
——, Heparin-coated circuits reduce postoperative lung complications in high-risk cardiac patients, Ranucci, M., *et al.*, (*EACTA*) A.71
——, Nausea and vomiting after cardiac surgery, Grebenik, C., *et al.*, (*EACTA*) A.76
——, Organ dysfunctions after cardiac surgery: definitions and prognosis, Calvert, B., *et al.*, (*EACTA*) A.78
Complications, abscess, Extradurals and infection, Brosnan, C. M., *et al.*, (*C*) 887–888
Complications, airway obstruction, Airway problems after carotid endarterectomy, Munro, F. J., *et al.* 156–159
——, Cervical haematoma and airway obstruction, Calder, I., *et al.*, (*C*) 888
——, Cervical haematoma and airway obstruction, Munro, F. J., *et al.*, (*C*) 888–889
Complications, awareness, Recall during intermittent propofol anaesthesia, Nordström, O., *et al.* 699–701
Complications, brain death, Oxygen consumption and delivery relationship in brain-dead organ donors, Langeron, O., *et al.* 783–789
Complications, cardiac arrest, Systolic pressure variation—a way to recognize dynamic hyperinflation, Myles, P. S., (*C*) 169
——, Systolic pressure variation—a way to recognize dynamic hyperinflation, Perel, A., *et al.*, (*C*) 168–169
Complications, cardiomyopathy, Cardiac arrest at induction of anaesthesia for Caesarean section, McIndoe, A. K., *et al.*, (*C*) 332–333
——, Cardiac arrest at induction of anaesthesia for Caesarean section, Wilson, J. A., (*C*) 332
Complications, cardioplegia, Arrhythmias after valvular surgery: a randomized double-blind Holter comparative

trial of St Thomas' (ST) *vs* CPS cardioplegia, VEDRINNE, C., *et al.*, (*EACTA*) A.66

Complications, catheter misplacement, Accidental insertion of an extradural catheter, FOX, A., *et al.*, (*C*) 336

——, Intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia, CAMANN, W., (*C*) 169

——, Intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia, LEE, J. S., *et al.*, (*C*) 169–170

——, Intrathecal insertion of an extradural catheter during combined spinal–extradural anaesthesia, ROBBINS, P. M., *et al.*, (*C*) 170

Complications, convulsions, Sevoflurane, enflurane and isoflurane have no persistent postanaesthetic effects on the central nervous system in cats, KURATA, J., *et al.* 721–725

Complications, diabetes, Blood lactate during cardiopulmonary bypass with a lactated priming solution, HETT, D., *et al.*, (*EACTA*) A.33

——, Use of i.v. insulin in well-controlled non-insulin-dependent diabetics undergoing major surgery, RAUCOULES-AIMÉ, M., *et al.* 198–202

Complications, Ehlers–Danlos syndrome, Myocardial ischaemia associated with Ehlers–Danlos syndrome, PRICE, C. M., *et al.* 464–466

Complications, embolism, Pulsed saline lavage causing venous air embolism in a patient with Paget's disease, SIDES, C. A. 330–331

——, Venous thromboembolism and cardiovascular surgery, BULLINGHAM, A., *et al.*, (*C*) 473

——, Venous thromboembolism and cardiovascular surgery, MCDONALD, D. S., (*C*) 473

Complications, emphysema, Stable right ventricular pressure-volume relation during lung volume reducing surgery for diffuse emphysema, GELINDER, S., *et al.*, (*EACTA*) A.80

Complications, endotoxaemia, Effect of low-dose dopamine on intestinal villus microcirculation during normotensive endotoxaemia in rats, SCHMIDT, H., *et al.* 707–712

Complications, fractured cricoid cartilage, Fracture of the cricoid cartilage after Sellick's manoeuvre, HEATH, K. J., *et al.* 877–878

Complications, haematoma, Venous thromboembolism and cardiovascular surgery, BULLINGHAM, A., *et al.*, (*C*) 473

——, Venous thromboembolism and cardiovascular surgery, MCDONALD, D. S., (*C*) 473

Complications, hypertension, Comparison of nicardipine, diltiazem and verapamil for controlling the cardiovascular responses to tracheal intubation, MIKAWA, K., *et al.* 221–226

——, Elective forceps delivery and extradural anaesthesia in a primigravida with portal hypertension and oesophageal varices, HERIOT, J. A., *et al.* 325–327

Complications, hypotension, Hydroxyethylstarch compared with modified gelatin as volume preload before spinal anaesthesia for Caesarean section, VERCAUTEREN, M. P., *et al.* 731–733

——, Hypotension during subarachnoid anaesthesia: haemodynamic effects of colloid and metaraminol, CRITCHLEY, L. A. H., *et al.* 734–736

——, Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for Caesarean section, THOMAS, D. G., *et al.* 61–65

Complications, hypothermia, Cerebral blood flow response to changes in CO$_2$ at hypothermia and normothermia. A controlled, randomized crossover study, WEYLAND, A., *et al.*, (*EACTA*) A.35

——, Continuous temperature and O$_2$ saturation monitoring of jugular blood during DHCA procedures for aortic surgery, PAINO, R., *et al.*, (*EACTA*) A.40

——, Effect of cooling on the force of contraction of rat and guineapig phrenic nerve hemidiaphragm preparations, ENGLAND, A. J., *et al.*, (*ARS*) 592–593P

——, Elevated serum levels of S-100 after deep hypothermic circulatory arrest correlate with duration of circulatory arrest, VAN DER LINDEN, J., *et al.*, (*EACTA*) A.84

Complications, inflammation, Phospholipase A$_2$ in cardiac surgery, HÅKANSON, E., *et al.*, (*EACTA*) A.1

Complications, Jehovah's Witness, Use of recombinant human erythropoietin to facilitate liver transplantation in a Jehovah's Witness, SNOOK, N. J., *et al.* 740–743

Complications, juvenile hyaline fibromatosis, Anaesthesia and juvenile hyaline fibromatosis, NORMAN, B., *et al.* 163–166

Complications, lung, Minimal incidence of reperfusion pulmonary oedema after pulmonary thromboendarterectomy, MARES, P., *et al.*, (*EACTA*) A.75

——, Non-invasive pressure support ventilation (NPSV) as an alternative to reintubation, PAULUS, S., *et al.*, (*EACTA*) A.73

Complications, morbidity, Reducing the potential morbidity of an unintentional spinal anaesthetic by aspirating cerebrospinal fluid, SOUTHORN, P., *et al.* 467–469

Complications, mucosal pressure, Laryngeal mask airway performance: effect of cuff deflation during anaesthesia, MORRIS, G. N., *et al.* 456–458

Complications, multiple organ dysfunction syndrome, Soluble E-cadherin concentrations in patients with systemic inflammatory response syndrome and multiorgan dysfunction syndrome, PITTARD, A. J., *et al.* 629–631

Complications, myalgia, Rocuronium pretreatment reduces suxamethonium-induced myalgia: comparison with vecuronium, FINDLAY, G. P., *et al.* 526–529

Complications, myopathy, Mivacurium chloride and late onset congenital myopathy, PARMAR, M., *et al.* 160–162

——, Suxamethonium in children, FARRELL, P. T., (*C*) 883–884

——, Suxamethonium in children, FIACCHINO, F., *et al.*, (*C*) 883

——, Suxamethonium in children, HOPKINS, P. M., (*C*) 884

Complications, neurological, Bilateral severe pain at L3–4 after spinal anaesthesia with hyperbaric 5% lignocaine, RODRÍGUEZ-CHINCHILLA, R., *et al.* 328–329

——, Maternal sequelae of childbirth, HUTTER, C. D. D., (*C*) 474

——, Maternal sequelae of childbirth, REYNOLDS, F., (*C*) 474–475

Complications, oesophageal varices, Elective forceps delivery and extradural anaesthesia in a primigravida with portal hypertension and oesophageal varices, HERIOT, J. A., *et al.* 325–327

Complications, overdose, Observations on patient-controlled administration of propofol, THORPE, S. J., *et al.*, (*ARS*) 576P

——, Patient-controlled propofol: randomized, double-blind dose refinement, SMITH, A. F., *et al.*, (*ARS*) 577P

Complications, Paget's disease, Pulsed saline lavage causing venous air embolism in a patient with Paget's disease, SIDES, C. A. 330–331

Complications, porphyria, Porphyria, propofol and rats, BÖHRER, H., (*C*) 172

——, Porphyria, propofol and rats, GORCHEIN, A., (*C*) 172

——, Porphyria, propofol and rats, TIDMARSH, M. D., (*C*) 171–172

Complications, pre-eclampsia, Management of pre-eclampsia, MUSHAMBI, M. C., *et al.*, (*C*) 889–890

——, Management of pre-eclampsia, WARD, J. E. H., *et al.*, (*C*) 889

——, Recent developments in the pathophysiology and management of pre-eclampsia, MUSHAMBI, M. C., *et al.* 133–148

——, Serotonin in pre-eclampsia, GAJRAJ, N. M., *et al.*, (*C*) 748–749

Complications, pressure sores, Anaemia and transfusion; major determinants of pressure sores after cardiac surgery, BAELE, PH., *et al.*, (*EACTA*) A.60

Complications, pulmonary oedema, Balloon mitral valve dilatation as an aid to weaning from ventilatory support in patients with intractable pulmonary oedema caused by severe mitral stenosis, DAVIS, G., *et al.* 879–880

Complications, regurgitation, Effect of pneumoperitoneum and Trendelenburg position on gastro–oesophageal reflux and lower oesophageal sphincter pressure, TOURNADRE, J. P., *et al.* 130–132

Complications, reperfusion syndrome, White blood cell cytosolic calcium changes during human orthotopic liver transplantation, ENRIGHT, S., *et al.*, (*ARS*) 587–588P

Complications, respiratory, Nebulized lignocaine before gaseous induction with desflurane, BUNTING, H. E., *et al.*, (*C*) 596

——, Nebulized lignocaine before gaseous induction with desflurane, NAY, P. G., (*C*) 596

Complications, sepsis syndrome, Sepsis-induced vasoparalysis does not involve the cerebral vasculature: indirect evidence from autoregulation and carbon dioxide reactivity studies, MATTA, B. F., *et al.* 790–794

Complications, septic shock, Prospects for management of peripheral vascular failure in septic shock, ALLEN, J. D., *et al.*, (*E*) 177–178

Complications, septicaemia, Soluble E-cadherin concentrations in patients with systemic inflammatory response syndrome and multiorgan dysfunction syndrome, PITTARD, A. J., *et al.* 629–631

Complications, smokers, Double-blind, randomized trial of cessation of smoking after audiotape suggestion during anaesthesia, MYLES, P. S., *et al.* 694–698

——, Effect of smoking on dose requirements for vecuronium, Teiriá, H., *et al.* 154–155

Complications, spontaneous excitatory movement, Unilateral convulsion after induction of anaesthesia with propofol, Cochran, D., *et al.* 570–572

Complications, stenosis, Balloon mitral valve dilatation as an aid to weaning from ventilatory support in patients with intractable pulmonary oedema caused by severe mitral stenosis, Davis, G., *et al.* 879–880

Complications, subarachnoid block, Sudden onset of subarachnoid block after subdural catheterization: a case of arachnoid rupture? Elliott, D. W., *et al.* 322–324

Complications, thrombosis, Venous thromboembolism and cardiovascular surgery, Bullingham, A., *et al.*, (*C*) 473

——, Venous thromboembolism and cardiovascular surgery, McDonald, D. S., (*C*) 473

Complications, tracheal bronchus, Airway management for patients with a tracheal bronchus, Ikeno, S., *et al.* 573–575

Complications, trauma, Prehospital monitoring of trauma patients: experience of a helicopter emergency medical service, Morley, A. P. 726–730

——, Transoesophageal echocardiography in chest trauma, George, S. J., (*C*) 336–337

——, Transoesophageal echocardiography in chest trauma, Kennedy, N., *et al.*, (*C*) 337

Complications, urinary retention, Spinal clonidine produces less urinary retention than spinal morphine, Gentili, M., *et al.* 872–873

Computers, Fuzzy logic control of inspired isoflurane and oxygen concentrations using minimal flow anaesthesia, Curatolo, M., *et al.* 245–250

Computers, fuzzy logic, Performance assessment of a fuzzy controller for atracurium-induced neuromuscular block, Mason, D. G., *et al.* 396–400

Coronary artery bypass surgery, Atrial natriuretic peptide (ANP) and N-terminal ANP: relationship to right ventricular function in patients undergoing coronary artery bypass surgery, Honkonen, E. L., *et al.*, (*EACTA*) A.6

Coronary artery disease, Assessment of right and left heart volume indices in patients undergoing coronary artery bypass surgery, Buhre, W., *et al.*, (*EACTA*) A.37

——, Effect of β-blockers *versus* calcium channel blockers in myocardial revascularization without cardiopulmonary bypass in pigs, Rajek, A., *et al.*, (*EACTA*) A.39

——, Free fatty acid (FFA) uptake immediately after routine coronary artery bypass surgery (CABG), Pietersen, H. G., *et al.*, (*EACTA*) A.2

——, Postoperative diastolic dysfunction. Incidence, natural history and prognosis, Oppizzi, M., *et al.*, (*EACTA*) A.46

——, Quality control of coronary bypass surgery: intraoperative transit time flow measurement, Walpoth, B. H., *et al.*, (*EACTA*) A.7

——, Transoesophageal echocardiography and haemodynamic monitoring in emergency surgical revascularization for extensive acute myocardial infarction, Guarracino, F., *et al.*, (*EACTA*) A.45

——, Use of internal mammary artery improves prognosis in patients under 70 undergoing combined valve and coronary artery surgery, Herijgers, P., *et al.*, (*EACTA*) A.79

Diabetes, Use of i.v. insulin in well-controlled non-insulin-dependent diabetics undergoing major surgery, Raucoules-Aimé, M., *et al.* 198–202

Difficult Hypertension: Practical Management and Decision Making, Kendall, M. J., *et al.*, (editors), (*R*) 891–892

Dog, Differential effects of desflurane and halothane on peripheral airway smooth muscle, Mazzeo, A. J., *et al.* 841–846

——, Effects and interactions of myocardial ischaemia and alterations in circulating blood volume on canine left ventricular diastolic function, Dalmas, S., *et al.* 419–427

——, Nitrous oxide and the rate of gas uptake from an unventilated lung in dogs, Joyce, C. J., *et al.* 292–296

Drug delivery, computerized, Prospective evaluation of pharmacokinetic model-controlled infusion of propofol in adult patients, Short, T. G., *et al.* 313–315

Drug delivery, transdermal, Effect of transdermal hyoscine on nausea and vomiting, Foster, R. N., (*C*) 749

——, Effect of transdermal hyoscine on nausea and vomiting, Honkavaara, P., (*C*) 749–750

——, Effect of transdermal hyoscine on nausea and vomiting during and after middle ear surgery under local anaesthesia, Honkavaara, P. 49–53

Ehlers–Danlos syndrome, Myocardial ischaemia associated with Ehlers–Danlos syndrome, Price, C. M., *et al.* 464–466

Embolism, air, Pulsed saline lavage causing venous air embolism in a patient with Paget's disease, Sides, C. A. 330–331

——, Venous air embolism: is end-tidal oxygen monitoring more informative than end-tidal carbon dioxide? Kyttä, J., *et al.*, (*C*) 475–476

——, Venous air embolism: is end-tidal oxygen monitoring more informative than end-tidal carbon dioxide? Mallick, A., *et al.*, (*C*) 475

Embolism, carbon dioxide, Effects of carbon dioxide embolism with nitrous oxide in the inspired gas in piglets, Nyarwaya, J.-B., *et al.* 428–434

Embolism, thromboembolism, Venous thromboembolism and cardiovascular surgery, Bullingham, A., *et al.*, (*C*) 473

——, Venous thromboembolism and cardiovascular surgery, McDonald, D. S., (*C*) 473

Enzymes, Elevated serum levels of S-100 after deep hypothermic circulatory arrest correlate with duration of circulatory arrest, van der Linden, J., *et al.*, (*EACTA*) A.84

Enzymes, phosphodiesterase, inhibition, Levosimendan is a more potent inotropic agent than amrinone after ischaemia in isolated perfused guinea pig hearts, Süzer, Ö., *et al.*, (*EACTA*) A.9

——, The efficacy of enoximone in improving the postoperative course of cardiac patients with severe myocardial dysfunction, Oppizzi, M., *et al.*, (*EACTA*) A.81

Enzymes, phospholipase C, Phospholipase A_2 in cardiac surgery, Håkanson, E., *et al.*, (*EACTA*) A.1

Enzymes, troponin I, Time course of serial serum troponin I levels after coronary artery bypass surgery (CABG), Filley, S., *et al.*, (*EACTA*) A.63

Enzymes, troponin T, Troponin-T for asessment of myocardial damage in CABG surgery, Dahlin, L. G., *et al.*, (*EACTA*) A.62

Epilepsy, Activation of the electrocorticogram by propofol during surgery for epilepsy, Smith, M., *et al.* 499–502

Equipment, Perioperative changes in receptors for ICAM-1/CD54 and immunglobulin G on monocytes by extracorporeal circulation (ECC), Hiesmayr, M., *et al.*, (*EACTA*) A.32

Equipment, assist device, The hemopump as left ventricular assist device in postcardiotomy heart failure, Meyns, B., *et al.*, (*EACTA*) A.38

Equipment, blankets, Convective warming combined with vasodilator therapy accelerates core rewarming after coronary artery bypass surgery, Harrison, S. J., *et al.* 511–514

Equipment, breathing systems, Accumulation of foreign gases during closed-system anaesthesia, Versichelen, L., *et al.* 668–672

——, Effect of apparatus on functional residual capacity, Drummond, G. B. 560–562

——, Efficiency of a circle system for short surgical cases: comparison of desflurane with isoflurane, Lee, D. J. H., *et al.* 780–782

——, Performance of vaporizers in circle systems (II), Royston, B., *et al.*, (*ARS*) 582–583P

Equipment, catheters extradural, Extradural and subarachnoid catheterization using the Seldinger technique, Delhaas, E. M. 149–150

——, Extradurals and infection, Brosnan, C. M., *et al.*, (*C*) 887–888

Equipment, catheters oximetry, Validation of the Edslab dual lumen oximetry catheter for continuous monitoring of jugular bulb oxygen saturation after severe head injury, Souter, M. J., *et al.* 744–746

Equipment, catheters subarachnoid, Extradural and subarachnoid catheterization using the Seldinger technique, Delhaas, E. M. 149–150

Equipment, gas analysers, Interference of volatile anaesthetics with infrared analysis of carbon dioxide and nitrous oxide tested in the Dräger Cicero EM using sevoflurane, Wilkes, A. R., *et al.* 737–739

Equipment, heart-lung machine, Comparative assessment of the biocompatibility of 4 types of tubing for cardiopulmonary bypass, Briquet, F., *et al.*, (*EACTA*) A.31

Equipment, hemopump, The hemopump as left ventricular assist device in postcardiotomy heart failure, Meyns, B., *et al.*, (*EACTA*) A.38

Equipment, masks anaesthesia, Cricoid pressure applied after placement of the laryngeal mask prevents gastric insufflation but inhibits ventilation, Asai, T., *et al.* 772–776

——, Dose of propofol for laryngeal mask airway insertion in children: effect of premedication with midazolam, Martlew, R. A., *et al.* 308–309

——, Effect of apparatus on functional residual capacity, Drummond, G. B. 560–562

——, Improving preoxygenation, McGowan, P., (*C*) 748

——, Improving preoxygenation, Smith, A. F., (*C*) 748
——, Laryngeal mask airway performance: effect of cuff deflation during anaesthesia, Morris, G. N., *et al.* 456–458
——, Midazolam before induction improves conditions for laryngeal mask insertion, Driver, I., *et al.*, (*e*) 175
——, Removal of the laryngeal mask airway in children: anaesthetized compared with awake, Kitching, A. J., *et al.* 874–876
Equipment, monitors, Prehospital monitoring of trauma patients: experience of a helicopter emergency medical service, Morley, A. P. 726–730
Equipment, perfusion system, A perfusion system for *in vitro* measurement of human cilia beat frequency, Selwyn, D. A., *et al.* 111–115
Equipment, pupillometer, Pupil changes during cardiopulmonary bypass, Fletcher, G. C., *et al.* 20–22
Equipment, temperature probes, Use of i.m. temperature probes during cardiopulmonary bypass in humans, Benson, J. P., *et al.*, (*C*) 472
——, Use of i.m. temperature probes during cardiopulmonary bypass in humans, Manners, J. M., (*C*) 471–472
Equipment, tubes tracheal, A new tracheal tube for difficult intubation, West, M. R. J., *et al.* 673–679
——, RAE tube obstruction during tonsil dissection, Graham, D., *et al.*, (*C*) 170–171
Equipment, vaporizers, Performance of vaporizers in circle systems (II), Royston, B., *et al.*, (*ARS*) 582–583P
Equipment, warming devices, Convective warming combined with vasodilator therapy accelerates core rewarming after coronary artery bypass surgery, Harrison, S. J., *et al.* 511–514
——, Delayed forced air warming prevents hypothermia during abdominal aortic surgery, Karayan, J., *et al.* 459–460
Errata, A model to describe the rate of oxyhaemoglobin desaturation during apnoea, Farmery, A. D., *et al.*, (*e*) 890
——, A multifactorial analysis to explain inadequate surgical analgesia after extradural block, Curatolo, M., *et al.*, (*e*) 598
——, Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine, Naguib, M., *et al.*, (*e*) 339
——, Midazolam before induction improves conditions for laryngeal mask insertion, Driver, I., *et al.*, (*e*) 175
Essentials of Anaesthetic Equipment, Al-Shaikh, B., *et al.*, (*R*) 751
Ethanol, Analysis of ethanol in expired air during low-flow isoflurane anaesthesia, Olsson, J., *et al.* 85–89
Eye, extraocular muscles, Effect of antagonism of mivacurium on recovery of extraocular muscle function, Mellor, D. J., *et al.* 621–623

Fluids, i.v., Haemodilution induces a hypercoagulable state, Ruttmann, T. G., *et al.* 412–414
——, Hydroxyethylstarch compared with modified gelatin as volume preload before spinal anaesthesia for Caesarean section, Vercauteren, M. P., *et al.* 731–733
——, Hypotension during subarachnoid anaesthesia: haemodynamic effects of colloid and metaraminol, Critchley, L. A. H., *et al.* 734–736
——, Inadvertent infusion of glucose saline into the extradural space, Mphanza, T., (*C*) 332
Free fatty acids, Free fatty acid (FFA) uptake immediately after routine coronary artery bypass surgery (CABG), Pietersen, H. G., *et al.*, (*EACTA*) A.2

Gases, non-anaesthetic, Kinetics of methaemoglobin and serum nitrogen oxide production during inhalation of nitric oxide in volunteers, Young, J. D., *et al.* 652–656
Gases non-anaesthetic, acetone, Accumulation of foreign gases during closed-system anaesthesia, Versichelen, L., *et al.* 668–672
Gases non-anaesthetic, carbon monoxide, Accumulation of foreign gases during closed-system anaesthesia, Versichelen, L., *et al.* 668–672
Gases non-anaesthetic, methane, Accumulation of foreign gases during closed-system anaesthesia, Versichelen, L., *et al.* 668–672
Gastrointestinal tract, antacids, Comparison of the effect of two dose schedules of oral omeprazole with oral ranitidine on gastric aspirate pH and volume in patients undergoing elective surgery, Levack, I. D., *et al.* 567–569
Gastrointestinal tract, circulation, Splanchnic blood flow during cardiopulmonary bypass assessed by indicator dilution technique, Gårdebäck, M., *et al.*, (*EACTA*) A.36
Gastrointestinal tract, intestine, Effect of low-dose dopamine on intestinal villus microcirculation during normotensive endotoxaemia in rats, Schmidt, H., *et al.* 707–712
Gastrointestinal tract, lower oesophageal sphincter, Effect of pneumoperitoneum and Trendelenburg position on gastro–oesophageal reflux and lower oesophageal sphincter pressure, Tournadre, J. P., *et al.* 130–132
Gastrointestinal tract, perfusion, The influence of dopaminergic agents on liver venous and mixed venous O_2-saturation in MODS – a preliminary report, Lampert, R., *et al.*, (*EACTA*) A.11
Gastrointestinal tract, pH, Comparison of the effect of two dose schedules of oral omeprazole with oral ranitidine on gastric aspirate pH and volume in patients undergoing elective surgery, Levack, I. D., *et al.* 567–569
——, Gastric tonometry, Boyd, O., *et al.*, (*C*) 750
——, Gastric tonometry to monitor tissue oxygenation: more than a gut feeling? Oh, T. E., (*E*) 604–605
——, Measurement technique and variation in intramucosal pH, Wood, P. R., *et al.* 563–564
——, Perioperative mucosal pH and splanchnic endotoxin concentration in orthotopic liver transplantation, Welte, M., *et al.* 90–98
Gastrointestinal tract, volume, Comparison of the effect of two dose schedules of oral omeprazole with oral ranitidine on gastric aspirate pH and volume in patients undergoing elective surgery, Levack, I. D., *et al.* 567–569
Genetic factors, proto-oncogenes, Nitrous oxide or halothane, or both, fail to suppress c-*fos* expression in rat spinal cord dorsal horn neurones after subcutaneous formalin, Sun, W. Z., *et al.* 99–105
——, Remembrance of times past: the significance of c-*fos* in pain, Munglani, R., *et al.*, (*E*) 1–4
Guineapig, Effect of cooling on the force of contraction of rat and guineapig phrenic nerve hemidiaphragm preparations, England, A. J., *et al.*, (*ARS*) 592–593P

Haemodynamics, Brain death induced haemodynamic failure in the rat is solely due to autonomic denervation, Herijgers, P., *et al.*, (*EACTA*) A.13
Haemofiltration, Pilot evaluation of RMI haemoconcentrator during cardiopulmonary bypass, Dhond, G., *et al.*, (*EACTA*) A.57
Haemoglobin, Standard pump flow rate and Sv_{O_2} above 60% do not imply adequate oxygen delivery during CPB, Ryckwaert, F., *et al.*, (*EACTA*) A.34
Handbook of Neonatal Anaesthesia, Hughes, D. G., *et al.*, (editors), (*R*) 599
Heart, Long chain triglycerides but not glucose–insulin, administered during reperfusion, improve recovery from stunning in isolated rabbit hearts, Van de Velde, M., *et al.*, (*EACTA*) A.3
——, Oxfenicine blocks the beneficial effects of intravenous long chain triglyceride (LCT) administration on regional myocardial stunning in conscious dogs, Van de Velde, M., *et al.*, (*EACTA*) A.4
Heart, arrhythmia, Arrhythmias after valvular surgery: a randomized double-blind Holter comparative trial of St Thomas' (ST) *vs* CPS cardioplegia, Vedrinne, C., *et al.*, (*EACTA*) A.66
——, Comparison of sotalol and digoxin in the prevention of early supraventricular arrhythmias after coronary artery bypass graft (CABG), Jadoul, J. L., *et al.*, (*EACTA*) A.67
——, QTc-dispersion in patients undergoing CABG surgery, Fruhwald, S., *et al.*, (*EACTA*) A.65
——, Trimetazidine does not reduce ischaemia-reperfusion induced arrhythmias in isolated perfused rat hearts, Süzer, Ö, *et al.*, (*EACTA*) A.68
Heart, cardiac output, Haemodynamic effects of air travel, Malagon, I., (*ARS*) 590P
Heart, cardiopulmonary bypass, Cardiopulmonary bypass with modified fluid gelatin and heparin-coated circuits, Jansen, P. G. M., *et al.* 13–19
——, Dobutamine increases oxygen consumption during constant flow cardiopulmonary bypass, Karzai, W., *et al.* 5–8
——, Effects of sevoflurane and isoflurane on systemic vascular resistance: use of cardiopulmonary bypass as a study model, Rödig, G., *et al.* 9–12
——, Plasma concentration and protein binding of propofol during cardiac surgery, Hammarén, E., *et al.*, (*EACTA*) A.16
——, Pupil changes during cardiopulmonary bypass, Fletcher, G. C., *et al.* 20–22
——, Remifentanil by infusion achieves predictable blood concentrations, Poulton, B. B., *et al.*, (*EACTA*) A.15
——, The effects of propofol on cerebral blood flow velocity and oxygenation during cardiopulmonary bypass, Ederberg, S., *et al.*, (*EACTA*) A.17
——, Use of i.m. temperature probes during cardiopulmonary bypass in humans, Benson, J. P., *et al.*, (*C*) 472

——, Use of i.m. temperature probes during cardiopulmonary bypass in humans, Manners, J. M., (*C*) 471–472
Heart, circulation, Serotonin induces coronary spasms after brain death in dogs, Herijgers, P., *et al.*, (*EACTA*) A.14
Heart, coronary artery disease, Effect of anaesthetic agents on pulmonary shunt during coronary artery surgery, Sindjelic, R., *et al.*, (*EACTA*) A.19
——, QTc-dispersion in patients undergoing CABG surgery, Fruhwald, S., *et al.*, (*EACTA*) A.65
Heart, diastolic function, Postoperative diastolic dysfunction. Incidence, natural history and prognosis, Oppizzi, M., *et al.*, (*EACTA*) A.46
Heart, digoxin, Comparison of sotalol and digoxin in the prevention of early supraventricular arrhythmias after coronary artery bypass graft (CABG), Jadoul, J. L., *et al.*, (*EACTA*) A.67
Heart, dobutamine, Dobutamine increases oxygen consumption during constant flow cardiopulmonary bypass, Karzai, W., *et al.* 5–8
Heart, dopamine, The influence of dopaminergic agents on liver venous and mixed venous O_2-saturation in MODS – a preliminary report, Lampert, R., *et al.*, (*EACTA*) A.11
Heart, dysfunction, The efficacy of enoximone in improving the postoperative course of cardiac patients with severe myocardial dysfunction, Oppizzi, M., *et al.*, (*EACTA*) A.81
Heart, failure, The hemopump as left ventricular assist device in postcardiotomy heart failure, Meyns, B., *et al.*, (*EACTA*) A.38
Heart, function, Assessment of right and left heart volume indices in patients undergoing coronary artery bypass surgery, Buhre, W., *et al.*, (*EACTA*) A.37
——, Postoperative diastolic dysfunction. Incidence, natural history and prognosis, Oppizzi, M., *et al.*, (*EACTA*) A.46
Heart, heart rate, Heart rate variability in patients recovering from general anaesthesia, Ireland, N., *et al.* 657–662
——, Periodic cardiovascular and ventilatory activity during midazolam sedation, Galletly, D. C., *et al.* 503–507
Heart, ischaemia, Effect of halothane on myocardial reoxygenation injury in the isolated rat heart, Schlack, W., *et al.* 860–867
——, Effects and interactions of myocardial ischaemia and alterations in circulating blood volume on canine left ventricular diastolic function, Dalmas, S., *et al.* 419–427
——, Levosimendan is a more potent inotropic agent than amrinone after ischaemia in isolated perfused guinea pig hearts, Süzer, Ö., *et al.*, (*EACTA*) A.9
——, Myocardial ischaemia and heart rate variability after coronary bypass surgery, Kentala, E., *et al.*, (*EACTA*) A.64
——, Myocardial ischaemia associated with Ehlers–Danlos syndrome, Price, C. M., *et al.* 464–466
——, Nitroglycerin induced hypoxaemia does not produce myocardial ischaemia, Toraman, F., *et al.*, (*EACTA*) A.21
Heart, isolated preparation, Effect of halothane on myocardial reoxygenation injury in the isolated rat heart, Schlack, W., *et al.* 860–867
——, Effects of morphine on atrial preparations obtained from non-failing and failing human hearts, Llobel, F., *et al.* 106–110
Heart, mitral valve, Changes of mitral inflow patterns as assessed by transoesophageal echocardiography following cardiac surgery: are they of clinical significance? Schmidlin, D., *et al.*, (*EACTA*) A.48
Heart, myocardial function, Comparison of the effects of urapidil and sodium nitroprusside on haemodynamic state, myocardial metabolism and function in patients during coronary artery surgery, van der Stroom, J. G., *et al.* 645–651
——, Effects and interactions of myocardial ischaemia and alterations in circulating blood volume on canine left ventricular diastolic function, Dalmas, S., *et al.* 419–427
——, Effects of morphine on atrial preparations obtained from non-failing and failing human hearts, Llobel, F., *et al.* 106–110
——, Effects of propofol and isoflurane on right ventricular function, Boyd, O., *et al.*, (*C*) 598
Heart, myocardial infarction, Perioperative myocardial infarction (PMI) in cardiac surgery—risk factors and clinical outcome, Svedjeholm, P., *et al.*, (*EACTA*) A.61
——, Time course of serial serum troponin I levels after coronary artery bypass surgery (CABG), Filley, S., *et al.*, (*EACTA*) A.63
Heart, myocardial injury, Effect of halothane on myocardial reoxygenation injury in the isolated rat heart, Schlack, W., *et al.* 860–867
Heart, myocardial protection, Effects of lidoflazine on left ventricular function, Deirue, G. L., *et al.*, (*EACTA*) A.10
Heart, myocardium, Experimental evaluation of a single breath inert gas technique for measurement of myocardial blood flow, Kazmaier, S., *et al.*, (*EACTA*) A.5
——, Nitroglycerin induced hypoxaemia does not produce myocardial ischaemia, Toraman, F., *et al.*, (*EACTA*) A.21
——, The effect of the calcium sensitizer levosimendan on normal and stunned left ventricular myocardium, Wetterings, C. J., *et al.*, (*EACTA*) A.8
Heart, rate, Myocardial ischaemia and heart rate variability after coronary bypass surgery, Kentala, E., *et al.*, (*EACTA*) A.64
Heart, right ventricular function, Atrial natriuretic peptide (ANP) and N-terminal ANP: relationship to right ventricular function in patients undergoing coronary artery bypass surgery, Honkonen, E. L., *et al.*, (*EACTA*) A.6
Heart, transplant, Haemodynamic effects of sodium nitroprusside *versus* prostaglandin E_1 in heart transplant candidates, Coddens, J., *et al.*, (*EACTA*) A.26
Heart, valve surgery, Use of internal mammary artery improves prognosis in patients under 70 undergoing combined valve and coronary artery surgery, Herijgers, P., *et al.*, (*EACTA*) A.79
Heart, ventricles, Effects and interactions of myocardial ischaemia and alterations in circulating blood volume on canine left ventricular diastolic function, Dalmas, S., *et al.* 419–427
Heart, ventricular function, Stable right ventricular pressure-volume relation during lung volume reducing surgery for diffuse emphysema, Gelinder, S., *et al.*, (*EACTA*) A.80
HELLP syndrome, Management of pre-eclampsia, Mushambi, M. C., *et al.*, (*C*) 889–890
——, Management of pre-eclampsia, Ward, J. E. H., *et al.*, (*C*) 889
——, Recent developments in the pathophysiology and management of pre-eclampsia, Mushambi, M. C., *et al.* 133–148
Histamine, Histamine release by neuromuscular blocking agents, Naguib, M., (*C*) 471
——, Histamine release by neuromuscular blocking agents, Todd, D. B., (*C*) 471
——, Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine, Naguib, M., *et al.*, (*e*) 339
——, Relaxant effect of ketamine and its isomers on histamine-induced contraction of tracheal smooth muscle, Hirota, K., *et al.* 266–270
Hormones, aldosterone, Laparoscopic cholecystectomy: haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position, O'Leary, E., *et al.* 640–644
Hormones, glucocorticoid, Metabolic and hormonal responses to induced hypotension for middle ear surgery, Newton, M. C., *et al.* 352–357
——, Methylprednisolone inhibits endotoxin-induced depression of contractile function in human arteries *in vitro*, Tsuneyoshi, I., *et al.* 251–257
Hormones, melatonin, Changes in pineal and pituitary hormone secretion under general anaesthesia, Reber, A., *et al.*, (*ARS*) 584P
Hormones, progesterone, CSF progesterone concentrations in pregnancy, Baliga, N., (*C*) 886
——, CSF progesterone concentrations in pregnancy, Hirabayashi, Y., *et al.*, (*C*) 886
Hormones, prostaglandins, Haemodynamic effects of sodium nitroprusside *versus* prostaglandin E_1 in heart transplant candidates, Coddens, J., *et al.*, (*EACTA*) A.26
——, Inhaled prostacyclin compared to inhaled nitric oxide in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance, Haraldsson, A., *et al.*, (*EACTA*) A.27
Hormones, renin, Laparoscopic cholecystectomy: haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position, O'Leary, E., *et al.* 640–644
Hypertension, Pharmacokinetics and haemodynamic effects of an ultrashort-acting calcium antagonist, Nordlander, M., *et al.*, (*EACTA*) A.24
Hypnotics benzodiazepine, diazepam, Hypotension following the administration of fentanyl-diazepam combination in chronic ACE inhibitor users, Özyurt, A., *et al.*, (*EACTA*) A.25
Hypnotics benzodiazepine, midazolam, Comparison of sedation with midazolam and ketamine: effects on airway muscle activity, Drummond, G. B. 663–667
——, Midazolam *vs* trimeprazine premedication for children during day-care surgery, Nathwani, D., *et al.*, (*ARS*) 589P
——, Periodic cardiovascular and ventilatory activity during midazolam sedation, Galletly, D. C., *et al.* 503–507

Hypnotics benzodiazepine, trimeprazine, Midazolam *vs* trimeprazine premedication for children during day-care surgery, Nathwani, D., *et al.*, (*ARS*) 589P
Hypnotics benzodiazepines, midazolam, Investigation into the effects of midazolam and propofol on human respiratory cilia beat frequency *in vitro*, Hann, H. C. L., *et al.*, (*ARS*) 591P
Hypotension, Relative effects of three hypotensive agents on pulmonary gas exchange, Van Oldenbeek, C., *et al.*, (*EACTA*) A.22
Hypothermia, Delayed forced air warming prevents hypothermia during abdominal aortic surgery, Karayan, J., *et al.* 459–460
——, Perioperative inadvertent hypothermia: what do we need to prevent? Carli, F., *et al.*, (*E*) 601–603
——, Preoperative infusion of amino acids prevents postoperative hypothermia, Selldén, E., *et al.* 227–234
Hypoxaemia, Postoperative sleep disturbances: mechanisms and clinical implications, Rosenberg-Adamsen, S., *et al.* 552–559
Hypoxia, Influence of oral clonidine on the ventilatory response to acute and sustained isocapnic hypoxia in human males, Foo, I. T., *et al.* 214–220
——, Slow ventilatory dynamics after isocapnic hypoxia and voluntary hyperventilation in humans: effects of isoflurane, Dahan, A., *et al.* 374–381

Immune response, Immunoglobulin and interleukin 2 production *ex vivo/in vitro* during treatment with oral retarded morphine, Palm, S., *et al.*, (*ARS*) 588–589P
Immune system, Perioperative changes in receptors for ICAM-1/CD54 and immunglobulin G on monocytes by extracorporeal circulation (ECC), Hiesmayr, M., *et al.*, (*EACTA*) A.32
Infants, Continuous extrapleural paravertebral infusion of bupivacaine for post-thoracotomy analgesia in young infants, Karmakar, M. K., *et al.* 811–815
——, Perioperative changes in α_1-acid glycoprotein concentrations in infants undergoing major surgery, Booker, P. D., *et al.* 365–368
——, Sevoflurane–nitrous oxide or halothane–nitrous oxide for paediatric bronchoscopy and gastroscopy, Meretoja, O. A., *et al.* 767–771
——, Vecuronium infusion requirements in paediatric patients in intensive care units: the use of acceleromyography, Hodges, U. M. 23–28
Infertility, Infertility among female hospital doctors in the UK, Maran, N. J., *et al.*, (*ARS*) 581P
Intensive care, A comparison of core temperature with thermal energy balance in predicting adequacy of rewarming from hypothermic cardiopulmonary bypass, Deakin, C. D., *et al.*, (*EACTA*) A.41
——, Comparison of the pharmacodynamics and pharmacokinetics of an infusion of *cis*-atracurium (51W89) or atracurium in critically ill patients undergoing mechanical ventilation in an intensive therapy unit, Boyd, A. H., *et al.* 382–388
——, Convective warming overcomes effects of cooling after cardiopulmonary bypass, Knowles, P. R., *et al.*, (*EACTA*) A.42
——, Gastric tonometry, Boyd, O., *et al.*, (*C*) 750
——, Haemodynamic effects of continued sedation during tracheal extubation, Conti, J., *et al.*, (*EACTA*) A.72
——, Oxygen consumption during early mobilization after CABG surgery in patients with normal cardiac function, Kirkeby-Garstad, I., *et al.*, (*EACTA*) A.74
——, Sepsis-induced vasoparalysis does not involve the cerebral vasculature: indirect evidence from autoregulation and carbon dioxide reactivity studies, Matta, B. F., *et al.* 790–794
——, Vecuronium infusion requirements in paediatric patients in intensive care units: the use of acceleromyography, Hodges, U. M. 23–28
Intensive Care: A Concise Textbook, 2nd Edn, Hind, C. J., *et al.*, (*R*) 599
Intensive care unit, Type of perioperative antihypertensive treatment delays extubation and prolongs ICU stay in cardiac surgery, Vuylsteke, A., *et al.*, (*EACTA*) A.30
Interactions (drugs), Volatile anaesthetics antagonize nitrous oxide and morphine-induced analgesia in the rat, Goto, T., *et al.* 702–706
Intubation tracheal, A new tracheal tube for difficult intubation, West, M. R. J., *et al.* 673–679
——, Airway management for patients with a tracheal bronchus, Ikeno, S., *et al.* 573–575
——, Evaluation of an oesophageal intubation detector device using electrical resistance, Deakin, C. D., (*ARS*) 590P
——, Failed intubation revisited: 17-yr experience in a teaching maternity unit, Hawthorne, L., *et al.* 680–684
——, RAE tube obstruction during tonsil dissection, Graham, D., *et al.*, (*C*) 170–171
Intubation tracheal, complications, A new tracheal tube for difficult intubation, West, M. R. J., *et al.* 673–679
Intubation tracheal, responses, Comparison of nicardipine, diltiazem and verapamil for controlling the cardiovascular responses to tracheal intubation, Mikawa, K., *et al.* 221–226
——, EEG arousal during laryngoscopy and intubation, Shannon, C., *et al.*, (*C*) 472
——, EEG arousal during laryngoscopy and intubation, Wilder-Smith, O. H. G., *et al.*, (*C*) 472–473
Intubation tracheal, training, A new tracheal tube for difficult intubation, West, M. R. J., *et al.* 673–679
Ions, calcium, Fentanyl increases intracellular Ca^{2+} concentrations in SH-SY5Y cells, Wandless, A. L., *et al.* 461–463
——, Is the dihydropyridine binding site on neuronal L-type calcium channels a target for i.v. anaesthetic agents? Hirota, K., *et al.*, (*ARS*) 591P
——, Voltage-sensitive Ca^{2+} channels and anaesthesia, Hirota, K., *et al.*, (*E*) 344–346
——, White blood cell cytosolic calcium changes during human orthotopic liver transplantation, Enright, S., *et al.*, (*ARS*) 587–588P
Ions, ion channels, Halothane and potassium channels in airway smooth muscle, Fukushima, T., *et al.* 847–853
——, Is the dihydropyridine binding site on neuronal L-type calcium channels a target for i.v. anaesthetic agents? Hirota, K., *et al.*, (*ARS*) 591P
Ions, ion channels, voltage-gated, Voltage-sensitive Ca^{2+} channels and anaesthesia, Hirota, K., *et al.*, (*E*) 344–346
Ions, magnesium, Electromyographic and mechanomyographic characteristics of neuromuscular block by magnesium sulphate in the pig, Lee, C., *et al.* 278–283
——, Magnesium sulphate enhances residual neuromuscular block induced by vecuronium, Fuchs-Buder, T., *et al.* 565–566
Ions, potassium, Halothane and potassium channels in airway smooth muscle, Fukushima, T., *et al.* 847–853

Kidney, blood flow, Preoperative inhibition of angiotensin-converting enzyme improves systemic and renal haemodynamic changes during aortic abdominal surgery, Licker, M., *et al.* 632–639
Kidney, function, Aprotinin treatment does not impair renal function during and after cardiac surgery, Schweizer, A., *et al.*, (*EACTA*) A.55
——, Preoperative inhibition of angiotensin-converting enzyme improves systemic and renal haemodynamic changes during aortic abdominal surgery, Licker, M., *et al.* 632–639

Lactate, Nitroglycerin induced hypoxaemia does not produce myocardial ischaemia, Toraman, F., *et al.*, (*EACTA*) A.21
Larynx, cricoid pressure, Cricoid pressure applied after placement of the laryngeal mask prevents gastric insufflation but inhibits ventilation, Asai, T., *et al.* 772–776
——, Fracture of the cricoid cartilage after Sellick's manoeuvre, Heath, K. J., *et al.* 877–878
Larynx, laryngoscopy, Airway management in cleft lip and palate surgery, Hatch, D. J., (*E*) 755–756
——, Difficult laryngoscopy in cleft lip and palate surgery, Gunawardana, R. H. 757–759
——, Effect of neuromuscular block on depth of anaesthesia as measured by the auditory evoked response, Richmond, C. E., *et al.* 446–448
Liver, Effects of dopamine and dopexamine on splanchnic microcirculation during major surgery in humans, Bellamy, M. C., *et al.*, (*ARS*) 587P
Liver, disease, Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation, De Wolf, A. M., *et al.* 624–628
Liver, failure, Early effects of total hepatectomy on haemodynamic state and organ uptake of catecholamines in the pig, James, M. F. M., *et al.* 713–720
Liver, oxygen, The influence of dopaminergic agents on liver venous and mixed venous O_2-saturation in MODS – a preliminary report, Lampert, R., *et al.*, (*EACTA*) A.11
Liver, transplantation, Aprotinin during liver transplantation, Cottam, S., *et al.*, (*C*) 882
——, Aprotinin during liver transplantation, Lentschener, C., *et al.*, (*C*) 882
——, Perioperative mucosal pH and splanchnic endotoxin

concentration in orthotopic liver transplantation, Welte, M., *et al.* 90–98
——, Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation, De Wolf, A. M., *et al.* 624–628
——, Use of recombinant human erythropoietin to facilitate liver transplantation in a Jehovah's Witness, Snook, N. J., *et al.* 740–743
Lung, atelectasis, Volumetric analysis of aeration in the lungs during general anaesthesia, Reber, A., *et al.* 760–766
Lung, circulation, Nitric oxide and pulmonary impedance, Poulton, B. B., *et al.*, (*EACTA*) A.29
Lung, compliance, Venous air embolism: is end-tidal oxygen monitoring more informative than end-tidal carbon dioxide? Kyttä, J., *et al.*, (*C*) 475–476
——, Venous air embolism: is end-tidal oxygen monitoring more informative than end-tidal carbon dioxide? Mallick, A., *et al.*, (*C*) 475
Lung, complications, Heparin-coated circuits reduce postoperative lung complications in high-risk cardiac patients, Ranucci, M., *et al.*, (*EACTA*) A.71
Lung, function, Nitric oxide and pulmonary impedance, Poulton, B. B., *et al.*, (*EACTA*) A.29
——, Relative effects of three hypotensive agents on pulmonary gas exchange, Van Oldenbeek, C., *et al.*, (*EACTA*) A.22
Lung, functional residual capacity, Changes in chest wall compartment volumes on induction of anaesthesia with eltanolone, propofol and thiopentone, Spens, H. J., *et al.* 369–373
——, Effect of apparatus on functional residual capacity, Drummond, G. B. 560–562
Lung, gas exchange, Nitrous oxide and the rate of gas uptake from an unventilated lung in dogs, Joyce, C. J., *et al.* 292–296
Lung, hyperinflation, Systolic pressure variation—a way to recognize dynamic hyperinflation, Myles, P. S., (*C*) 169
——, Systolic pressure variation—a way to recognize dynamic hyperinflation, Perel, A., *et al.*, (*C*) 168–169
Lung, hypertension, Correlation of predicted and recorded concentrations of nitric oxide during long-term inhalation in infants after cardiac surgery, Knapik, P., *et al.*, (*EACTA*) A.28
——, Inhaled prostacyclin compared to inhaled nitric oxide in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance, Haraldsson, Å., *et al.*, (*EACTA*) A.27
Lung, metabolic function, Pulmonary uptake of sufentanil during and after constant rate infusion, Boer, F., *et al.* 203–208
Lung, pathophysiology, Investigation into the effects of midazolam and propofol on human respiratory cilia beat frequency *in vitro*, Hann, H. C. L., *et al.*, (*ARS*) 591P
——, Pulmonary lactate flux after cardiopulmonary bypass, Kulkarni, V., *et al.*, (*ARS*) 586P
Lung, shunt, Effect of anaesthetic agents on pulmonary shunt during coronary artery surgery, Sindjelic, R., *et al.*, (*EACTA*) A.19
Lung, surgery, Minimal incidence of reperfusion pulmonary oedema after pulmonary thromboendarterectomy, Mares, P., *et al.*, (*EACTA*) A.75
Lung, trachea, A perfusion system for *in vitro* measurement of human cilia beat frequency, Selwyn, D. A., *et al.* 111–115
——, Effects of 3 MAC of halothane, enflurane and isoflurane on cilia beat frequency of human nasal epithelium *in vitro*, Raphael, J. H., *et al.* 116–121
——, Effects of morphine on human nasal cilia beat frequency *in vitro*, Selwyn, D. A., *et al.* 274–277
——, Halothane and potassium channels in airway smooth muscle, Fukushima, T., *et al.* 847–853
——, Recovery of respiratory ciliary function after depression by inhalation anaesthetic agents: an *in vitro* study using nasal turbinate explants, Raphael, J. H., *et al.* 854–859
Lung, volume, Changes in chest wall compartment volumes on induction of anaesthesia with eltanolone, propofol and thiopentone, Spens, H. J., *et al.* 369–373
——, Effect of apparatus on functional residual capacity, Drummond, G. B. 560–562
600 MCQs in Anaesthesia: Clinical Practice, 2nd Edn, Goodman, N. W., *et al.*, (*R*) 751

Measurement techniques, Assessment of right and left heart volume indices in patients undergoing coronary artery bypass surgery, Buhre, W., *et al.*, (*EACTA*) A.37
——, Splanchnic blood flow during cardiopulmonary bypass assessed by indicator dilution technique, Gårdebäck, M., *et al.*, (*EACTA*) A.36
Measurement techniques, acceleromyography, Vecuronium infusion requirements in paediatric patients in intensive care units: the use of acceleromyography, Hodges, U. M. 23–28
Measurement techniques, arterial pressure, Radial artery tonometry: moderately accurate but unpredictable technique of continuous non-invasive arterial pressure measurement, Weiss, B. M., *et al.* 405–411
Measurement techniques, blood flow, A new method for cerebral blood flow measurement, Mielck, F., *et al.*, (*EACTA*) A.12
Measurement techniques, calorimetry, Oxygen consumption and delivery relationship in brain-dead organ donors, Langeron, O., *et al.* 783–789
Measurement techniques, Doppler ultrasound, Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for Caesarean section, Thomas, D. G., *et al.* 61–65
Measurement techniques, drug concentration, Comparison of arterialized venous with arterial blood propofol concentrations during sub-anaesthetic infusions in volunteers, Johnston, K. R., *et al.* 401–404
Measurement techniques, echocardiography, Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for Caesarean section, Thomas, D. G., *et al.* 61–65
Measurement techniques, electromyography, Effect of isoflurane and sevoflurane on the magnitude and time course of neuromuscular block produced by vecuronium, pancuronium and atracurium, Vanlinthout, L. E. H., *et al.* 389–395
——, Electromyographic and mechanomyographic characteristics of neuromuscular block by magnesium sulphate in the pig, Lee, C., *et al.* 278–283
——, Evoked EMG response during inhalation of a subanaesthetic concentration of isoflurane, Polhill, S. L., *et al.*, (*ARS*) 578P
——, Magnesium sulphate enhances residual neuromuscular block induced by vecuronium, Fuchs-Buder, T., *et al.* 565–566
——, Post-tetanic constant stimulus train patterns during neuromuscular block with atracurium and vecuronium, Bryan, A., *et al.*, (*ARS*) 579P
Measurement techniques, gas exchange, Experimental evaluation of a single breath inert gas technique for measurement of myocardial blood flow, Kazmaier, S., *et al.*, (*EACTA*) A.5
Measurement techniques, mechanomyography, Effect of isoflurane and sevoflurane on the magnitude and time course of neuromuscular block produced by vecuronium, pancuronium and atracurium, Vanlinthout, L. E. H., *et al.* 389–395
——, Electromyographic and mechanomyographic characteristics of neuromuscular block by magnesium sulphate in the pig, Lee, C., *et al.* 278–283
Measurement techniques, near infrared spectroscopy, Use of near infrared spectroscopy to estimate cerebral blood flow in conscious and anaesthetized adult subjects, Owen-Reece, H., *et al.* 43–48
Measurement techniques, nuclear magnetic resonance, Anatomical configuration of the spinal column in the supine position. III. Comparison of adolescent and adult volunteers, Hirabayashi, Y., *et al.* 508–510
——, Magnetic resonance imaging of the superior vena cava during spontaneous respiration with continuous positive airway pressure via a facemask in normal subjects, Mayor, A. H., *et al.*, (*ARS*) 578–579P
Measurement techniques, oscillometry, Radial artery tonometry: moderately accurate but unpredictable technique of continuous non-invasive arterial pressure measurement, Weiss, B. M., *et al.* 405–411
Measurement techniques, oximetry, Validation of the Edslab dual lumen oximetry catheter for continuous monitoring of jugular bulb oxygen saturation after severe head injury, Souter, M. J., *et al.* 744–746
Measurement techniques, plethysmography, Periodic cardiovascular and ventilatory activity during midazolam sedation, Galletly, D. C., *et al.* 503–507
Measurement techniques, pupil diameter, Pupil changes during cardiopulmonary bypass, Fletcher, G. C., *et al.* 20–22
Measurement techniques, spectrometry, Accumulation of foreign gases during closed-system anaesthesia, Versichelen, L., *et al.* 668–672
Measurement techniques, spectrophotometry, Interference of volatile anaesthetics with infrared analysis of carbon dioxide and nitrous oxide tested in the Dräger Cicero EM using sevoflurane, Wilkes, A. R., *et al.* 737–739

Measurement techniques, thrombelastography, Haemodilution induces a hypercoagulable state, Ruttmann, T. G., *et al.* 412–414

Measurement techniques, tomography, Volumetric analysis of aeration in the lungs during general anaesthesia, Reber, A., *et al.* 760–766

Measurement techniques, tonometry, Radial artery tonometry: moderately accurate but unpredictable technique of continuous non-invasive arterial pressure measurement, Weiss, B. M., *et al.* 405–411

Measurement techniques, transit time flow, Quality control of coronary bypass surgery: intraoperative transit time flow measurement, Walpoth, B. H., *et al.*, (*EACTA*) A.7

Measurement techniques, transoesophageal echocardiography, Changes of mitral inflow patterns as assessed by transoesophageal echocardiography following cardiac surgery: are they of clinical significance? Schmidlin, D., *et al.*, (*EACTA*) A.48

——, Does perioperative transoesophageal echocardiography change the therapy of cardiothoracic patients? Brase, R., *et al.*, (*EACTA*) A.47

——, Doppler-derived left ventricular DP/DT: peroperative feasibility of the method during mitral valve surgery, Broka, S., *et al.*, (*EACTA*) A.44

——, Echocardiography by the anaesthetist: a French survey, Lehot, J. J., *et al.*, (*EACTA*) A.43

——, Epiaortic scanning of the ascending aorta identifies arteriosclerotic plaques and changes surgical practice during CABG? van der Linden, J., *et al.*, (*EACTA*) A.82

——, Postoperative diastolic dysfunction. Incidence, natural history and prognosis, Oppizzi, M., *et al.*, (*EACTA*) A.46

——, Transoesophageal echocardiography and haemodynamic monitoring in emergency surgical revascularization for extensive acute myocardial infarction, Guarracino, F., *et al.*, (*EACTA*) A.45

——, Transoesophageal echocardiography and intraoperative evaluation of left ventricular performance, Jovic, M., *et al.*, (*EACTA*) A.49

Measurement techniques, transthoracic electrical impedance, Haemodynamic effects of moderate normovolaemic haemodilution in conscious and anaesthetized patients, Biboulet, P., *et al.* 81–84

——, Hypotension during subarachnoid anaesthesia: haemodynamic effects of colloid and metaraminol, Critchley, L. A. H., *et al.* 734–736

Measurement techniques, ultrasound, Sepsis-induced vasoparalysis does not involve the cerebral vasculature: indirect evidence from autoregulation and carbon dioxide reactivity studies, Matta, B. F., *et al.* 790–794

Memory, Double-blind, randomized trial of cessation of smoking after audiotape suggestion during anaesthesia, Myles, P. S., *et al.* 694–698

——, Effect of tramadol on depth of anaesthesia, Coetzee, J. F., *et al.* 415–418

——, Heart rate variability in patients recovering from general anaesthesia, Ireland, N., *et al.* 657–662

——, Is there implicit memory after propofol sedation? Cork, R. C., *et al.* 492–498

——, Isolated forearm technique, Healy, T. E. J., *et al.*, (*C*) 885–886

——, Isolated forearm technique, Russell, I. F., *et al.*, (*C*) 884–885

——, Omitting nitrous oxide in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials, Tramèr, M., *et al.* 186–193

——, Recall during intermittent propofol anaesthesia, Nordström, O., *et al.* 699–701

Metabolism, Oxygen consumption during early mobilization after CABG surgery in patients with normal cardiac function, Kirkeby-Garstad, I., *et al.*, (*EACTA*) A.74

Metabolism, fasting, Preoperative fasting for paediatric anaesthesia, Hopp, M., (*C*) 471

——, Preoperative fasting for paediatric anaesthesia, Phillips, S., *et al.*, (*C*) 471

Metabolism, glucose, Metabolic and hormonal responses to induced hypotension for middle ear surgery, Newton, M. C., *et al.* 352–357

——, Use of i.v. insulin in well-controlled non-insulin-dependent diabetics undergoing major surgery, Raucoules-Aimé, M., *et al.* 198–202

Metabolism, insulin, Use of i.v. insulin in well-controlled non-insulin-dependent diabetics undergoing major surgery, Raucoules-Aimé, M., *et al.* 198–202

Metabolism, lactate, Blood lactate during cardiopulmonary bypass with a lactated priming solution, Hett, D., *et al.*, (*EACTA*) A.33

——, Pulmonary lactate flux after cardiopulmonary bypass, Kulkarni, V., *et al.*, (*ARS*) 586P

Metabolism, myocardial, Free fatty acid (FFA) uptake immediately after routine coronary artery bypass surgery (CABG), Pietersen, H. G., *et al.*, (*EACTA*) A.2

Metabolism, triglycerides, Long chain triglycerides but not glucose–insulin, administered during reperfusion, improve recovery from stunning in isolated rabbit hearts, Van de Velde, M., *et al.*, (*EACTA*) A.3

——, Oxfenicine blocks the beneficial effects of intravenous long chain triglyceride (LCT) administration on regional myocardial stunning in conscious dogs, Van de Velde, M., *et al.*, (*EACTA*) A.4

Mitral valve, Doppler-derived left ventricular DP/DT: peroperative feasibility of the method during mitral valve surgery, Broka, S., *et al.*, (*EACTA*) A.44

Model, computer simulation, Fuzzy logic control of inspired isoflurane and oxygen concentrations using minimal flow anaesthesia, Curatolo, M., *et al.* 245–250

Model, dog, Oxfenicine blocks the beneficial effects of intravenous long chain triglyceride (LCT) administration on regional myocardial stunning in conscious dogs, Van de Velde, M., *et al.*, (*EACTA*) A.4

——, Serotonin induces coronary spasms after brain death in dogs, Herijgers, P., *et al.*, (*EACTA*) A.14

Model, guineapig, Levosimendan is a more potent inotropic agent than amrinone after ischaemia in isolated perfused guinea pig hearts, Süzer, Ö., *et al.*, (*EACTA*) A.9

Model, heart, Effect of halothane on myocardial reoxygenation injury in the isolated rat heart, Schlack, W., *et al.* 860–867

Model, logistic regression, Prediction of postoperative nausea and vomiting using a logistic regression model, Toner, C. C., *et al.* 347–351

Model, neuroblastoma cells, Fentanyl increases intracellular Ca^{2+} concentrations in SH-SY5Y cells, Wandless, A. L., *et al.* 461–463

——, Interaction of i.v. anaesthetic agents with 5-HT_3 receptors, Appadu, B. L., *et al.* 271–273

Model, pharmaco-physiological, A model to describe the rate of oxyhaemoglobin desaturation during apnoea, Farmery, A. D., *et al.* 284–291

——, A model to describe the rate of oxyhaemoglobin desaturation during apnoea, Farmery, A. D., *et al.*, (*e*) 890

Model, rabbit, Long chain triglycerides but not glucose–insulin, administered during reperfusion, improve recovery from stunning in isolated rabbit hearts, Van de Velde, M., *et al.*, (*EACTA*) A.3

Model, rat, Brain death induced haemodynamic failure in the rat is solely due to autonomic denervation, Herijgers, P., *et al.*, (*EACTA*) A.13

——, Is the dihydropyridine binding site on neuronal L-type calcium channels a target for i.v. anaesthetic agents? Hirota, K., *et al.*, (*ARS*) 591P

——, Porphyria, propofol and rats, Böhrer, H., (*C*) 172

——, Porphyria, propofol and rats, Gorchein, A., (*C*) 172

——, Porphyria, propofol and rats, Tidmarsh, M. D., (*C*) 171–172

——, Trimetazidine does not reduce ischaemia-reperfusion induced arrhythmias in isolated perfused rat hearts, Süzer, Ö, *et al.*, (*EACTA*) A.68

Modulation of the Inflammatory Response in Severe Sepsis, Tellado, J. M., *et al.*, (editors), (*R*) 173–174

Monitoring, Transoesophageal echocardiography and haemodynamic monitoring in emergency surgical revascularization for extensive acute myocardial infarction, Guarracino, F., *et al.*, (*EACTA*) A.45

Monitoring, echocardiography, Balloon mitral valve dilatation as an aid to weaning from ventilatory support in patients with intractable pulmonary oedema caused by severe mitral stenosis, Davis, G., *et al.* 879–880

——, Transoesophageal echocardiography in chest trauma, George, S. J., (*C*) 336–337

——, Transoesophageal echocardiography in chest trauma, Kennedy, N., *et al.*, (*C*) 337

Monitoring, electrocardiography, Laparoscopic cholecystectomy: haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position, O'Leary, E., *et al.* 640–644

Monitoring, electrocorticography, Activation of the electrocorticogram by propofol during surgery for epilepsy, Smith, M., *et al.* 499–502

Monitoring, electroencephalography, EEG arousal during laryngoscopy and intubation, Shannon, C., *et al.*, (*C*) 472

——, EEG arousal during laryngoscopy and intubation, Wilder-Smith, O. H. G., *et al.*, (*C*) 472–473

——, Haemodynamic responses to incision and sternotomy in relation to the auditory evoked potential and spontaneous EEG, DE BEER, N. A. M., *et al.* 685–693

Monitoring, evoked potentials, Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by evoked potentials, ROTH, D., *et al.* 38–42

——, Central nuclei and spinal pathways in feedback inhibitory spinal cord potentials in ketamine-anaesthetized rats, DENDA, S., *et al.* 258–265

——, Effect of neuromuscular block on depth of anaesthesia as measured by the auditory evoked response, RICHMOND, C. E., *et al.* 446–448

——, Effect of suxamethonium on the auditory evoked response in humans, BRUNNER, M. D., *et al.* 34–37

——, Evoked potentials challenge the concept of Adamkiewicz's artery, VUYLSTEKE, A., *et al.*, (*EACTA*) A.50

——, Haemodynamic responses to incision and sternotomy in relation to the auditory evoked potential and spontaneous EEG, DE BEER, N. A. M., *et al.* 685–693

——, Remifentanil reduces auditory and somatosensory evoked responses during isoflurane anaesthesia in a dose-dependent manner, CRABB, I., *et al.* 795–801

——, Suxamethonium and auditory evoked potentials, BRUNNER, M. D., *et al.*, (*C*) 881

——, Suxamethonium and auditory evoked potentials, PONTE, J., (*C*) 881

——, Total i.v. anaesthesia for transcranial magnetic evoked potential spinal cord monitoring, WATT, J. W. H., *et al.* 870–871

Monitoring, neuromuscular function, Vecuronium infusion requirements in paediatric patients in intensive care units: the use of acceleromyography, HODGES, U. M. 23–28

Monitoring, oxygen, Venous air embolism: is end-tidal oxygen monitoring more informative than end-tidal carbon dioxide? KYTTÄ, J., *et al.*, (*C*) 475–476

——, Venous air embolism: is end-tidal oxygen monitoring more informative than end-tidal carbon dioxide? MALLICK, A., *et al.*, (*C*) 475

Monitoring, oxygen saturation, Validation of the Edslab dual lumen oximetry catheter for continuous monitoring of jugular bulb oxygen saturation after severe head injury, SOUTER, M. J., *et al.* 744–746

Monitoring, pH gastric, Gastric tonometry, BOYD, O., *et al.*, (*C*) 750

Monitoring, pH oesophageal, Gastric tonometry to monitor tissue oxygenation: more than a gut feeling? OH, T. E., (*E*) 604–605

——, Measurement technique and variation in intramucosal pH, WOOD, P. R., *et al.* 563–564

——, Perioperative mucosal pH and splanchnic endotoxin concentration in orthotopic liver transplantation, WELTE, M., *et al.* 90–98

Monitoring, spirometry, Venous air embolism: is end-tidal oxygen monitoring more informative than end-tidal carbon dioxide? KYTTÄ, J., *et al.*, (*C*) 475–476

——, Venous air embolism: is end-tidal oxygen monitoring more informative than end-tidal carbon dioxide? MALLICK, A., *et al.*, (*C*) 475

Monitoring, temperature, Convective warming combined with vasodilator therapy accelerates core rewarming after coronary artery bypass surgery, HARRISON, S. J., *et al.* 511–514

——, Delayed forced air warming prevents hypothermia during abdominal aortic surgery, KARAYAN, J., *et al.* 459–460

——, Perioperative inadvertent hypothermia: what do we need to prevent? CARLI, F., *et al.*, (*E*) 601–603

Monitoring, temperature, rewarming, Convective warming overcomes effects of cooling after cardiopulmonary bypass, KNOWLES, P. R., *et al.*, (*EACTA*) A.42

Monitoring, tonometry, Gastric tonometry to monitor tissue oxygenation: more than a gut feeling? OH, T. E., (*E*) 604–605

Monocytes, Perioperative changes in receptors for ICAM-1/CD54 and immunglobulin G on monocytes by extracorporeal circulation (ECC), HIESMAYR, M., *et al.*, (*EACTA*) A.32

Muscle respiratory, Changes in chest wall compartment volumes on induction of anaesthesia with eltanolone, propofol and thiopentone, SPENS, H. J., *et al.* 369–373

Muscle vascular, responses, Effects of propofol on rabbit mesenteric arteries and veins, KAMITANI, K., (*C*) 333–334

——, Effects of propofol on rabbit mesenteric arteries and veins, STRATFORD, N., (*C*) 333

Nerve, Effect of stimulation rate on force of contraction in partially paralysed rat phrenic nerve hemidiaphragm preparations, RICHARDS, K., *et al.*, (*ARS*) 579–580P

Nerve, damage, Ulnar and common peroneal nerve block revisited, SOUTER, A. J., *et al.*, (*C*) 595–596

Neuro-anaesthetic Practice, VAN AKEN, H., (editor), (*R*) 599

Neuromuscular Block, FELDMAN, S., (*R*) 893

Neuromuscular block, Effect of neuromuscular block on depth of anaesthesia as measured by the auditory evoked response, RICHMOND, C. E., *et al.* 446–448

——, Effect of stimulation rate on force of contraction in partially paralysed rat phrenic nerve hemidiaphragm preparations, RICHARDS, K., *et al.*, (*ARS*) 579–580P

Neuromuscular block, 51W89, Comparison of the pharmacodynamics and pharmacokinetics of an infusion of *cis*-atracurium (51W89) or atracurium in critically ill patients undergoing mechanical ventilation in an intensive therapy unit, BOYD, A. H., *et al.* 382–388

——, Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation, DE WOLF, A. M., *et al.* 624–628

Neuromuscular block, α-bungarotoxin, Effect of stimulation rate on force of contraction in partially paralysed rat phrenic nerve hemidiaphragm preparations, RICHARDS, K., *et al.*, (*ARS*) 579–580P

Neuromuscular block, antagonism, Effect of antagonism of mivacurium on recovery of extraocular muscle function, MELLOR, D. J., *et al.* 621–623

Neuromuscular block, atracurium, Comparison of the pharmacodynamics and pharmacokinetics of an infusion of *cis*-atracurium (51W89) or atracurium in critically ill patients undergoing mechanical ventilation in an intensive therapy unit, BOYD, A. H., *et al.* 382–388

——, Effect of isoflurane and sevoflurane on the magnitude and time course of neuromuscular block produced by vecuronium, pancuronium and atracurium, VANLINTHOUT, L. E. H., *et al.* 389–395

——, Histamine release by neuromuscular blocking agents, NAGUIB, M., (*C*) 471

——, Histamine release by neuromuscular blocking agents, TODD, D. B., (*C*) 471

——, Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine, NAGUIB, M., *et al.*, (*e*) 339

——, Performance assessment of a fuzzy controller for atracurium-induced neuromuscular block, MASON, D. G., *et al.* 396–400

——, Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation, DE WOLF, A. M., *et al.* 624–628

——, Post-tetanic constant stimulus train patterns during neuromuscular block with atracurium and vecuronium, BRYAN, A., *et al.*, (*ARS*) 579P

Neuromuscular block, hexamethonium, Effect of stimulation rate on force of contraction in partially paralysed rat phrenic nerve hemidiaphragm preparations, RICHARDS, K., *et al.*, (*ARS*) 579–580P

Neuromuscular block, interaction, Modelling the interaction of two neuromuscular blocking agents: generation of an additive or a supra-additive neuromuscular block, NIGROVIC, V., *et al.*, (*ARS*) 580–581P

Neuromuscular block, measurement of response, Electromyographic and mechanomyographic characteristics of neuromuscular block by magnesium sulphate in the pig, LEE, C., *et al.* 278–283

——, Evoked EMG response during inhalation of a subanaesthetic concentration of isoflurane, POLHILL, S. L., *et al.*, (*ARS*) 578P

——, Factors governing onset of neuromuscular block, AUDIBERT, G., *et al.*, (*C*) 597–598

——, Factors governing onset of neuromuscular block, FELDMAN, S., *et al.*, (*C*) 596–597

Neuromuscular block, mivacurium, Edrophonium antagonism of intense mivacurium-induced neuromuscular block in children, ABDULATIF, M., *et al.* 239–244

——, Effect of antagonism of mivacurium on recovery of extraocular muscle function, MELLOR, D. J., *et al.* 621–623

——, Histamine release by neuromuscular blocking agents, NAGUIB, M., (*C*) 471

——, Histamine release by neuromuscular blocking agents, TODD, D. B., (*C*) 471

——, Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine, NAGUIB, M., *et al.*, (*e*) 339

——, Mivacurium chloride and late onset congenital myopathy, PARMAR, M., *et al.* 160–162

——, Onset time of neuromuscular block is determined by the pharmacokinetics of the blocking drug, BEAUFORT, A. M., *et al.*, (*ARS*) 580P

——, Time course of potentiation of mivacurium by halothane and isoflurane in children, MERETOJA, O. A., *et al.* 235–238

Neuromuscular block, pancuronium, Effect of isoflurane and sevoflurane on the magnitude and time course of neuromuscular block produced by vecuronium, pancuronium and atracurium, Vanlinthout, L. E. H., *et al.* 389–395

Neuromuscular block, recovery, Magnesium sulphate enhances residual neuromuscular block induced by vecuronium, Fuchs-Buder, T., *et al.* 565–566

Neuromuscular block, rocuronium, Histamine release by neuromuscular blocking agents, Naguib, M., (*C*) 471

——, Histamine release by neuromuscular blocking agents, Todd, D. B., (*C*) 471

——, Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine, Naguib, M., *et al.*, (*e*) 339

——, Pharmacokinetics of rocuronium after bolus and continuous infusion during halothane anaesthesia, McCoy, E. P., *et al.* 29–33

——, Rocuronium pretreatment reduces suxamethonium-induced myalgia: comparison with vecuronium, Findlay, G. P., *et al.* 526–529

——, Rocuronium: the newest aminosteroid neuromuscular blocking drug, Hunter, J. M., (*E*) 481–483

Neuromuscular block, suxamethonium, Effect of suxamethonium on the auditory evoked response in humans, Brunner, M. D., *et al.* 34–37

——, Factors governing onset of neuromuscular block, Audibert, G., *et al.*, (*C*) 597–598

——, Factors governing onset of neuromuscular block, Feldman, S., *et al.*, (*C*) 596–597

——, Onset time of neuromuscular block is determined by the pharmacokinetics of the blocking drug, Beaufort, A. M., *et al.*, (*ARS*) 580P

——, Rocuronium pretreatment reduces suxamethonium-induced myalgia: comparison with vecuronium, Findlay, G. P., *et al.* 526–529

——, Suxamethonium and auditory evoked potentials, Brunner, M. D., *et al.*, (*C*) 881

——, Suxamethonium and auditory evoked potentials, Ponte, J., (*C*) 881

——, Suxamethonium in children, Farrell, P. T., (*C*) 883–884

——, Suxamethonium in children, Fiacchino, F., *et al.*, (*C*) 883

——, Suxamethonium in children, Hopkins, P. M., (*C*) 884

Neuromuscular block, tubocurarine, Histamine release by neuromuscular blocking agents, Naguib, M., (*C*) 471

——, Histamine release by neuromuscular blocking agents, Todd, D. B., (*C*) 471

——, Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine, Naguib, M., *et al.*, (*e*) 339

Neuromuscular block, vecuronium, Effect of isoflurane and sevoflurane on the magnitude and time course of neuromuscular block produced by vecuronium, pancuronium and atracurium, Vanlinthout, L. E. H., *et al.* 389–395

——, Effect of neuromuscular block on depth of anaesthesia as measured by the auditory evoked response, Richmond, C. E., *et al.* 446–448

——, Effect of smoking on dose requirements for vecuronium, Teiriä, H., *et al.* 154–155

——, Effect of stimulation rate on force of contraction in partially paralysed rat phrenic nerve hemidiaphragm preparations, Richards, K., *et al.*, (*ARS*) 579–580P

——, Factors governing onset of neuromuscular block, Audibert, G., *et al.*, (*C*) 597–598

——, Factors governing onset of neuromuscular block, Feldman, S., *et al.*, (*C*) 596–597

——, Histamine release by neuromuscular blocking agents, Naguib, M., (*C*) 471

——, Histamine release by neuromuscular blocking agents, Todd, D. B., (*C*) 471

——, Histamine-release haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine, Naguib, M., *et al.*, (*e*) 339

——, Magnesium sulphate enhances residual neuromuscular block induced by vecuronium, Fuchs-Buder, T., *et al.* 565–566

——, Post-tetanic constant stimulus train patterns during neuromuscular block with atracurium and vecuronium, Bryan, A., *et al.*, (*ARS*) 579P

——, Rocuronium pretreatment reduces suxamethonium-induced myalgia: comparison with vecuronium, Findlay, G. P., *et al.* 526–529

——, Vecuronium infusion requirements in paediatric patients in intensive care units: the use of acceleromyography, Hodges, U. M. 23–28

Neuromuscular transmission, Effect of cooling on the force of contraction of rat and guineapig phrenic nerve hemidiaphragm preparations, England, A. J., *et al.*, (*ARS*) 592–593P

——, Evoked EMG response during inhalation of a subanaesthetic concentration of isoflurane, Polhill, S. L., *et al.*, (*ARS*) 578P

Operating rooms, contamination, Occupational x-ray exposure of anaesthetists, McGowan, C., *et al.* 868–869

Ophthalmic Anaesthesia—A Practical Handbook, 2nd Edn, Smith, G. B., *et al.*, (*R*) 891

Organ failure, Organ dysfunctions after cardiac surgery: definitions and prognosis, Calvert, B., *et al.*, (*EACTA*) A.78

Organization, Use of blood products in cardiovascular surgery 4 years after the Sanguis study, Deneys, V., *et al.*, (*EACTA*) A.56

Oxygen, consumption, Dobutamine increases oxygen consumption during constant flow cardiopulmonary bypass, Karzai, W., *et al.* 5–8

——, Oxygen consumption and delivery relationship in brain-dead organ donors, Langeron, O., *et al.* 783–789

——, Oxygen consumption during early mobilization after CABG surgery in patients with normal cardiac function, Kirkeby-Garstad, I., *et al.*, (*EACTA*) A.74

Oxygen, delivery, Oxygen consumption and delivery relationship in brain-dead organ donors, Langeron, O., *et al.* 783–789

Oxygen, delivery systems, Standard pump flow rate and Sv_{O_2} above 60% do not imply adequate oxygen delivery during CPB, Ryckwaert, F., *et al.*, (*EACTA*) A.34

Oxygen, inspired concentration, Nitrous oxide and the rate of gas uptake from an unventilated lung in dogs, Joyce, C. J., *et al.* 292–296

Oxygen, saturation, A model to describe the rate of oxyhaemoglobin desaturation during apnoea, Farmery, A. D., *et al.* 284–291

——, A model to describe the rate of oxyhaemoglobin desaturation during apnoea, Farmery, A. D., *et al.*, (*e*) 890

——, Validation of the Edslab dual lumen oximetry catheter for continuous monitoring of jugular bulb oxygen saturation after severe head injury, Souter, M. J., *et al.* 744–746

Oxygen, tissue, Gastric tonometry to monitor tissue oxygenation: more than a gut feeling? Oh, T. E., (*E*) 604–605

Oxygen, uptake, Carbon dioxide output in laparoscopic cholecystectomy, Kazama, T., *et al.* 530–535

Paediatrics, Comparison of caudally administered morphine *vs* hydromorphone in paediatric cardiac surgical patients, Lavoie, J., *et al.*, (*EACTA*) A.70

——, Correlation of predicted and recorded concentrations of nitric oxide during long-term inhalation in infants after cardiac surgery, Knapik, P., *et al.*, (*EACTA*) A.28

Pain, A multifactorial analysis to explain inadequate surgical analgesia after extradural block, Curatolo, M., *et al.*, (*e*) 598

Pain, experimental, Analgesic effect in humans of subanaesthetic isoflurane concentrations evaluated by evoked potentials, Roth, D., *et al.* 38–42

Pain, mechanism, Analgesic and anti-inflammatory effects of lignocaine–prilocaine (EMLA) cream in human burn injury, Pedersen, J. L., *et al.* 806–810

——, Antinociceptive actions of intrathecal xylazine: interactions with spinal cord opioid pathways, Goodchild, C. S., *et al.* 544–551

——, Effect of systemic *N*-methyl-D-aspartate receptor antagonist (ketamine) on primary and secondary hyperalgesia in humans, Ilkjaer, S., *et al.* 829–834

Pain, postoperative, Absence of an early pre-emptive effect after thoracic extradural bupivacaine in thoracic surgery, Aguilar, J. L., *et al.* 72–76

——, Comparison of i.v. and s.c. diamorphine infusions for the treatment of acute pain in children, Semple, D., *et al.* 310–312

——, Continuous extradural infusion of ropivacaine for prevention of postoperative pain after major orthopaedic surgery, Turner, G., *et al.* 606–610

——, Continuous extrapleural paravertebral infusion of bupivacaine for post-thoracotomy analgesia in young infants, Karmakar, M. K., *et al.* 811–815

——, Does pre-incisional thoracic extradural block combined with diclofenac reduce postoperative pain after abdominal hysterectomy? Espinet, A., *et al.* 209–213

——, Effect of systemic *N*-methyl-D-aspartate receptor antagonist (ketamine) on primary and secondary hyperalgesia in humans, Ilkjaer, S., *et al.* 829–834

——, Influence of dose and timing of administration of morphine on postoperative pain and analgesic requirements, Mansfield, M. D., *et al.* 358–361

——, Naproxen after day-case laparoscopic sterilization, DUNN, T. J., *et al.*, (*C*) 168
——, Naproxen after day-case laparoscopic sterilization, WILLIAMS, P. I., (*C*) 168
——, Surgical pain is followed not only by spinal sensitization but also by supraspinal antinociception, WILDER-SMITH, O. H. G., *et al.* 816–821
Pain, threshold, Surgical pain is followed not only by spinal sensitization but also by supraspinal antinociception, WILDER-SMITH, O. H. G., *et al.* 816–821
Pain, visceral, Visceral pain during Caesarean section, FAIRFIELD, M. C., (*C*) 167
——, Visceral pain during Caesarean section, HIRABAYASHI, Y., *et al.*, (*C*) 167
Pharmacodynamics, Comparison of the pharmacodynamics and pharmacokinetics of an infusion of *cis*-atracurium (51W89) or atracurium in critically ill patients undergoing mechanical ventilation in an intensive therapy unit, BOYD, A. H., *et al.* 382–388
——, Modelling the interaction of two neuromuscular blocking agents: generation of an additive or a supra-additive neuromuscular block, NIGROVIC, V., *et al.*, (*ARS*) 580–581P
——, Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation, DE WOLF, A. M., *et al.* 624–628
——, Pharmacokinetics of rocuronium after bolus and continuous infusion during halothane anaesthesia, MCCOY, E. P., *et al.* 29–33
——, Time course of potentiation of mivacurium by halothane and isoflurane in children, MERETOJA, O. A., *et al.* 235–238
Pharmacokinetics, Analysis of ethanol in expired air during low-flow isoflurane anaesthesia, OLSSON, J., *et al.* 85–89
——, Pharmacokinetics and haemodynamic effects of an ultrashort-acting calcium antagonist, NORDLANDER, M., *et al.*, (*EACTA*) A.24
——, Plasma concentration and protein binding of propofol during cardiac surgery, HAMMARÉN, E., *et al.*, (*EACTA*) A.16
——, Remifentanil by infusion achieves predictable blood concentrations, POULTON, B. B., *et al.*, (*EACTA*) A.15
Pharmacokinetics, 51W89, Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation, DE WOLF, A. M., *et al.* 624–628
Pharmacokinetics, aprotinin, Aprotinin treatment does not impair renal function during and after cardiac surgery, SCHWEIZER, A., *et al.*, (*EACTA*) A.55
Pharmacokinetics, atracurium, Comparison of the pharmacodynamics and pharmacokinetics of an infusion of *cis*-atracurium (51W89) or atracurium in critically ill patients undergoing mechanical ventilation in an intensive therapy unit, BOYD, A. H., *et al.* 382–388
——, Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation, DE WOLF, A. M., *et al.* 624–628
Pharmacokinetics, bupivacaine, Smaller children have greater bupivacaine plasma concentrations after ilioinguinal block, SMITH, T., *et al.* 452–455
Pharmacokinetics, models, Prospective evaluation of pharmacokinetic model-controlled infusion of propofol in adult patients, SHORT, T. G., *et al.* 313–315
Pharmacokinetics, remifentanil, Remifentanil—an opioid for the 21st century, THOMPSON, J. P., *et al.*, (*E*) 341–343
Pharmacokinetics, rocuronium, Pharmacokinetics of rocuronium after bolus and continuous infusion during halothane anaesthesia, MCCOY, E. P., *et al.* 29–33
Pharmacokinetics, stereoisomers, Comparison of the pharmacodynamics and pharmacokinetics of an infusion of *cis*-atracurium (51W89) or atracurium in critically ill patients undergoing mechanical ventilation in an intensive therapy unit, BOYD, A. H., *et al.* 382–388
——, Pharmacokinetics and pharmacodynamics of cisatracurium in patients with end-stage liver disease undergoing liver transplantation, DE WOLF, A. M., *et al.* 624–628
——, Relaxant effect of ketamine and its isomers on histamine-induced contraction of tracheal smooth muscle, HIROTA, K., *et al.* 266–270
Pharmacokinetics, sulfentanil, Pulmonary uptake of sufentanil during and after constant rate infusion, BOER, F., *et al.* 203–208
Pharmacology, ACE inhibitors, Preoperative inhibition of angiotensin-converting enzyme improves systemic and renal haemodynamic changes during aortic abdominal surgery, LICKER, M., *et al.* 632–639
Pharmacology, cadherin, Soluble E-cadherin concentrations in patients with systemic inflammatory response syndrome and multiorgan dysfunction syndrome, PITTARD, A. J., *et al.* 629–631
Pharmacology, clonidine, Extradural clonidine provides adjunctive pain relief without sedation for women in labour, TREMLETT, M. R., *et al.*, (*ARS*) 583–584P
——, Influence of oral clonidine on the ventilatory response to acute and sustained isocapnic hypoxia in human males, FOO, I. T., *et al.* 214–220
Pharmacology, dexamethasone, Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting, LÓPEZ-OLAONDO, L., *et al.* 835–840
Pharmacology, glibenclamide, Effect of phosphodiesterase inhibitors on human arteries *in vitro*, VROOM, M. B., *et al.* 122–129
Pharmacology, nitric oxide, Correlation of predicted and recorded concentrations of nitric oxide during long-term inhalation in infants after cardiac surgery, KNAPIK, P., *et al.*, (*EACTA*) A.28
——, Effect of phosphodiesterase inhibitors on human arteries *in vitro*, VROOM, M. B., *et al.* 122–129
——, Inhaled prostacyclin compared to inhaled nitric oxide in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance, HARALDSSON, A., *et al.*, (*EACTA*) A.27
——, Kinetics of methaemoglobin and serum nitrogen oxide production during inhalation of nitric oxide in volunteers, YOUNG, J. D., *et al.* 652–656
——, Nitric oxide and pulmonary impedance, POULTON, B. B., *et al.*, (*EACTA*) A.29
——, Prospects for management of peripheral vascular failure in septic shock, ALLEN, J. D., *et al.*, (*E*) 177–178
Pharmacology, ondansetron, Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting, LÓPEZ-OLAONDO, L., *et al.* 835–840
——, Comparison of ondansetron and prochlorperazine for the prevention of nausea and vomiting after adenotonsillectomy, VAN DEN BERG, A. A. 449–451
Pharmacology, phosphodiesterase inhibitors, Effect of phosphodiesterase inhibitors on human arteries *in vitro*, VROOM, M. B., *et al.* 122–129
Pharmacology, prochlorperazine, Comparison of ondansetron and prochlorperazine for the prevention of nausea and vomiting after adenotonsillectomy, VAN DEN BERG, A. A. 449–451
Pharmacology, remifentanil, Remifentanil—an opioid for the 21st century, THOMPSON, J. P., *et al.*, (*E*) 341–343
Pharmacology, sodium nitroprusside, Comparison of the effects of urapidil and sodium nitroprusside on haemodynamic state, myocardial metabolism and function in patients during coronary artery surgery, VAN DER STROOM, J. G., *et al.* 645–651
Pharmacology, steady-state infusions, Comparison of arterialized venous with arterial blood propofol concentrations during sub-anaesthetic infusions in volunteers, JOHNSTON, K. R., *et al.* 401–404
Pharmacology, urapidil, Comparison of the effects of urapidil and sodium nitroprusside on haemodynamic state, myocardial metabolism and function in patients during coronary artery surgery, VAN DER STROOM, J. G., *et al.* 645–651
Pig, Early effects of total hepatectomy on haemodynamic state and organ uptake of catecholamines in the pig, JAMES, M. F. M., *et al.* 713–720
——, Effect of pneumoperitoneum and Trendelenburg position on gastro-oesophageal reflux and lower oesophageal sphincter pressure, TOURNADRE, J. P., *et al.* 130–132
——, Effects of carbon dioxide embolism with nitrous oxide in the inspired gas in piglets, NYARWAYA, J.-B., *et al.* 428–434
——, Electromyographic and mechanomyographic characteristics of neuromuscular block by magnesium sulphate in the pig, LEE, C., *et al.* 278–283
——, Onset time of neuromuscular block is determined by the pharmacokinetics of the blocking drug, BEAUFORT, A. M., *et al.*, (*ARS*) 580P
Polypeptides, aprotinin, Aprotinin during liver transplantation, COTTAM, S., *et al.*, (*C*) 882
——, Aprotinin during liver transplantation, LENTSCHENER, C., *et al.*, (*C*) 882
Polypeptides, endotoxin, Methylprednisolone inhibits endotoxin-induced depression of contractile function in human arteries *in vitro*, TSUNEYOSHI, I., *et al.* 251–257
Position, effects, Laparoscopic cholecystectomy: haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position, O'LEARY, E., *et al.* 640–644
Position, supine, Anatomical configuration of the spinal column in the supine position. III. Comparison of

adolescent and adult volunteers, Hirabayashi, Y., *et al.* 508–510

Position, Trendelenburg, Effect of pneumoperitoneum and Trendelenburg position on gastro-oesophageal reflux and lower oesophageal sphincter pressure, Tournadre, J. P., *et al.* 130–132

——, Laparoscopic cholecystectomy: haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position, O'Leary, E., *et al.* 640–644

Potency, anaesthetic, MAC, Effect of age on MAC in humans: a meta-analysis, Mapleson, W. W. 179–185

Pregnancy, Maternal sequelae of childbirth, Hutter, C. D. D., (*C*) 474

——, Maternal sequelae of childbirth, Reynolds, F., (*C*) 474–475

Premedication, Midazolam *vs* trimeprazine premedication for children during day-care surgery, Nathwani, D., *et al.*, (*ARS*) 589P

Premedication, hyoscine, Effect of transdermal hyoscine on nausea and vomiting, Foster, R. N., (*C*) 749

——, Effect of transdermal hyoscine on nausea and vomiting, Honkavaara, P., (*C*) 749–750

——, Effect of transdermal hyoscine on nausea and vomiting during and after middle ear surgery under local anaesthesia, Honkavaara, P. 49–53

Premedication, midazolam, Dose of propofol for laryngeal mask airway insertion in children: effect of premedication with midazolam, Martlew, R. A., *et al.* 308–309

Primer of Intraoperative Neurophysiologic Monitoring, Russell, G. B., *et al.*, (editors), (*R*) 477

Principles and Practice Series: *Respiratory Support*, Sykes, K., (*R*) 338

Protein, α_1-acid glycoprotein, Perioperative changes in α_1-acid glycoprotein concentrations in infants undergoing major surgery, Booker, P. D., *et al.* 365–368

Protein, amino acids, Preoperative infusion of amino acids prevents postoperative hypothermia, Selldén, E., *et al.* 227–234

Protein, cytokines, Predictability of tumour necrosis factor concentration: evidence for a mechanism for mutual regulation of autacoids in systemic inflammatory response syndrome, Pittard, A. J., *et al.*, (*ARS*) 587P

Protein, immunoglobulins, Immunoglobulin and interleukin 2 production *ex vivo*/*in vitro* during treatment with oral retarded morphine, Palm, S., *et al.*, (*ARS*) 588–589P

Proteins, Atrial natriuretic peptide (ANP) and N-terminal ANP: relationship to right ventricular function in patients undergoing coronary artery bypass surgery, Honkonen, E. L., *et al.*, (*EACTA*) A.6

Psychological responses, Parental or anaesthetist's ability to predict a 'stormy' induction in young children, Lyons, B., *et al.*, (*ARS*) 589P

——, Psychological characteristics and patient-controlled analgesia, Thomas, V. J., *et al.*, (*C*) 595

Psychological responses, postoperative, Cognitive failures after general anaesthesia for day-case surgery, Tzabar, Y., *et al.* 194–197

Publications, Impact factors in anaesthesia journals, Smith, G., (*E*) 753–754

——, The 11th World Congress of Anaesthesiology, Smith, G., (*E*) 479–480

Rabbit, Effects of propofol on rabbit mesenteric arteries and veins, Kamitani, K., (*C*) 333–334

——, Effects of propofol on rabbit mesenteric arteries and veins, Stratford, N., (*C*) 333

Rat, Central nuclei and spinal pathways in feedback inhibitory spinal cord potentials in ketamine-anaesthetized rats, Denda, S., *et al.* 258–265

——, Effect of cooling on the force of contraction of rat and guineapig phrenic nerve hemidiaphragm preparations, England, A. J., *et al.*, (*ARS*) 592–593P

——, Effect of halothane on myocardial reoxygenation injury in the isolated rat heart, Schlack, W., *et al.* 860–867

——, Effect of low-dose dopamine on intestinal villus microcirculation during normotensive endotoxaemia in rats, Schmidt, H., *et al.* 707–712

——, Effect of stimulation rate on force of contraction in partially paralysed rat phrenic nerve hemidiaphragm preparations, Richards, K., *et al.*, (*ARS*) 579–580P

——, Nitrous oxide or halothane, or both, fail to suppress c-*fos* expression in rat spinal cord dorsal horn neurones after subcutaneous formalin, Sun, W. Z., *et al.* 99–105

——, Porphyria, propofol and rats, Böhrer, H., (*C*) 172

——, Porphyria, propofol and rats, Gorchein, A., (*C*) 172

——, Porphyria, propofol and rats, Tidmarsh, M. D., (*C*) 171–172

——, Volatile anaesthetics antagonize nitrous oxide and morphine-induced analgesia in the rat, Goto, T., *et al.* 702–706

Receptors, cholinergic, Differential effects of desflurane and halothane on peripheral airway smooth muscle, Mazzeo, A. J., *et al.* 841–846

Receptors, opioid, Effects of morphine on human nasal cilia beat frequency *in vitro*, Selwyn, D. A., *et al.* 274–277

——, Fentanyl increases intracellular Ca^{2+} concentrations in SH-SY5Y cells, Wandless, A. L., *et al.* 461–463

——, Use of regional i.v. morphine analgesia in patients undergoing total knee arthroplasty, Corbett, A. R., *et al.*, (*ARS*) 593–594P

Receptors, postsynaptic, Effect of stimulation rate on force of contraction in partially paralysed rat phrenic nerve hemidiaphragm preparations, Richards, K., *et al.*, (*ARS*) 579–580P

Receptors, presynaptic, Effect of stimulation rate on force of contraction in partially paralysed rat phrenic nerve hemidiaphragm preparations, Richards, K., *et al.*, (*ARS*) 579–580P

Recovery, Org 21465 a new i.v. anaesthetic agent, Daniell, C. J., *et al.*, (*ARS*) 586–587P

Recovery, postoperative, Heart rate variability in patients recovering from general anaesthesia, Ireland, N., *et al.* 657–662

Regional Anesthesia: An Atlas of Anatomy and Techniques, Hahn, M. B., *et al.*, (editors), (*R*) 751

Rewarming, A comparison of core temperature with thermal energy balance in predicting adequacy of rewarming from hypothermic cardiopulmonary bypass, Deakin, C. D., *et al.*, (*EACTA*) A.41

Risk factors, Does Parsonnet score predict the usefulness of Sv_{O_2} pulmonary artery catheter (Sv_{O_2}PAC) during heart surgery? Vedrinne, C., *et al.*, (*EACTA*) A.85

——, Scoring systems *versus* subjective assessment as an outcome predictor in adult cardiac surgery, Smith, E., *et al.*, (*EACTA*) A.86

Sedation, Evaluation of bispectral index as an objective sedation score in the intensive care unit, Pearson, A. J., *et al.*, (*ARS*) 577–578P

Sedation and Analgesia in the Critically Ill, Park, G. R., *et al.*, (editors), (*R*) 174

Serotonin (5-hydroxytryptamine), Interaction of i.v. anaesthetic agents with 5-HT_3 receptors, Appadu, B. L., *et al.* 271–273

——, Serotonin in pre-eclampsia, Gajraj, N. M., *et al.*, (*C*) 748–749

Sleep, Postoperative sleep disturbances: mechanisms and clinical implications, Rosenberg-Adamsen, S., *et al.* 552–559

Sleep, postoperative, Postoperative sleep disturbances: mechanisms and clinical implications, Rosenberg-Adamsen, S., *et al.* 552–559

Spinal cord, Antinociceptive actions of intrathecal xylazine: interactions with spinal cord opioid pathways, Goodchild, C. S., *et al.* 544–551

——, Evoked potentials challenge the concept of Adamkiewicz's artery, Vuylsteke, A., *et al.*, (*EACTA*) A.50

Spinal cord, evoked potentials, Central nuclei and spinal pathways in feedback inhibitory spinal cord potentials in ketamine-anaesthetized rats, Denda, S., *et al.* 258–265

——, Total i.v. anaesthesia for transcranial magnetic evoked potential spinal cord monitoring, Watt, J. W. H., *et al.* 870–871

Statistics, A pitfall in the use of the Altman nomogram for power estimation, Evans, M. J., *et al.*, (*C*) 334

Statistics, cusum, Measurement of competence, Goodman, N. W., (*C*) 750

Strabismus, Prevention of vomiting after paediatric strabismus surgery, Morton, N. S., (*C*) 473

——, Prevention of vomiting after paediatric strabismus surgery, Tramèr, M., *et al.*, (*C*) 473–474

Surgery, Is tramadol better than ketorolac after day-case laparoscopy? Sabar, M. A., *et al.*, (*ARS*) 584P

Surgery, abdominal, Postoperative analgesia by continuous extradural infusion of ropivacaine after upper abdominal surgery, Schug, S. A., *et al.* 487–491

Surgery, aneurysm, Myocardial ischaemia associated with Ehlers–Danlos syndrome, Price, C. M., *et al.* 464–466

Surgery, aortic, Epiaortic scanning of the ascending aorta identifies arteriosclerotic plaques and changes surgical practice during CABG? van der Linden, J., *et al.*, (*EACTA*) A.82

Surgery, cardiovascular, Comparison of the effects of urapidil and sodium nitroprusside on haemodynamic state, myocardial metabolism and function in patients during coronary artery surgery, van der Stroom, J. G., *et al.* 645–651

——, Convective warming combined with vasodilator therapy accelerates core rewarming after coronary artery bypass surgery, HARRISON, S. J., *et al.* 511–514
—, Haemodynamic responses to incision and sternotomy in relation to the auditory evoked potential and spontaneous EEG, DE BEER, N. A. M., *et al.* 685–693
—, Pulmonary lactate flux after cardiopulmonary bypass, KULKARNI, V., *et al.*, (*ARS*) 586P
—, Use of i.m. temperature probes during cardiopulmonary bypass in humans, BENSON, J. P., *et al.*, (*C*) 472
—, Use of i.m. temperature probes during cardiopulmonary bypass in humans, MANNERS, J. M., (*C*) 471–472
Surgery, day-case, Midazolam *vs* trimeprazine premedication for children during day-care surgery, NATHWANI, D., *et al.*, (*ARS*) 589P
Surgery, emergency, Transoesophageal echocardiography [illegible] nd haemodynamic monitoring in emergency surgical [illegible] scularization for extensive acute myocardial infarction, [illegible] RACINO, F., *et al.*, (*EACTA*) A.45
[illegible] **ndarterectomy**, Airway problems after carotid [illegible] ectomy, MUNRO, F. J., *et al.* 156–159
[illegible] haematoma and airway obstruction, CALDER, I., [illegible] 888
[illegible] haematoma and airway obstruction, MUNRO, [illegible]., (*C*) 888–889
[illegible] **oscopy**, Sevoflurane–nitrous oxide or [illegible] e–nitrous oxide for paediatric bronchoscopy and [illegible] copy, MERETOJA, O. A., *et al.* 767–771
[illegible] **facial**, Regional anaesthesia for outpatient nasal [illegible] gery, MOLLIEX, S., *et al.* 151–153
[illegible] **y, gynaecological**, Combination of ondansetron and [illegible] xamethasone in the prophylaxis of postoperative nausea [illegible] d vomiting, LÓPEZ-OLAONDO, L., *et al.* 835–840
[illegible] oes pre-incisional thoracic extradural block combined [illegible] h diclofenac reduce postoperative pain after abdominal [illegible] sterectomy? ESPINET, A., *et al.* 209–213
[illegible] Influence of dose and timing of administration of morphine on postoperative pain and analgesic requirements, MANSFIELD, M. D., *et al.* 358–361
——, Naproxen after day-case laparoscopic sterilization, DUNN, T. J., *et al.*, (*C*) 168
——, Naproxen after day-case laparoscopic sterilization, WILLIAMS, P. I., (*C*) 168
Surgery, hepatic, Early effects of total hepatectomy on haemodynamic state and organ uptake of catecholamines in the pig, JAMES, M. F. M., *et al.* 713–720
Surgery, hormonal response, Laparoscopic cholecystectomy: haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position, O'LEARY, E., *et al.* 640–644
urgery, laparoscopy, Carbon dioxide output in laparoscopic cholecystectomy, KAZAMA, T., *et al.* 530–535
—, Effect of pneumoperitoneum and Trendelenburg position on gastro-oesophageal reflux and lower oesophageal sphincter pressure, TOURNADRE, J. P., *et al.* 130–132
——, Laparoscopic cholecystectomy: haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position, O'LEARY, E., *et al.* 640–644
Surgery, lung, Stable right ventricular pressure-volume relation during lung volume reducing surgery for diffuse emphysema, GELINDER, S., *et al.*, (*EACTA*) A.80
Surgery, ophthalmological, Day-case cataract surgery, GOOLD, J. E., (*C*) 333
——, Day-case cataract surgery, MALTBY, J. R., *et al.*, (*C*) 333
——, Prevention of vomiting after paediatric strabismus surgery, MORTON, N. S., (*C*) 473
——, Prevention of vomiting after paediatric strabismus surgery, TRAMÈR, M., *et al.*, (*C*) 473–474
Surgery, orthopaedic, Continuous extradural infusion of ropivacaine for prevention of postoperative pain after major orthopaedic surgery, TURNER, G., *et al.* 606–610
——, Use of regional i.v. morphine analgesia in patients undergoing total knee arthroplasty, CORBETT, A. R., *et al.*, (*ARS*) 593–594P
Surgery, otolaryngological, Comparison of ondansetron and prochlorperazine for the prevention of nausea and vomiting after adenotonsillectomy, VAN DEN BERG, A. A. 449–451
——, Effect of ondansetron on nausea and vomiting after middle ear surgery during general anaesthesia, HONKAVAARA, P. 316–318
——, Effect of transdermal hyoscine on nausea and vomiting, FOSTER, R. N., (*C*) 749
——, Effect of transdermal hyoscine on nausea and vomiting, HONKAVAARA, P., (*C*) 749–750
——, Effect of transdermal hyoscine on nausea and vomiting during and after middle ear surgery under local anaesthesia, HONKAVAARA, P. 49–53
——, Metabolic and hormonal responses to induced hypotension for middle ear surgery, NEWTON, M. C., *et al.* 352–357
——, RAE tube obstruction during tonsil dissection, GRAHAM, D., *et al.*, (*C*) 170–171
Surgery, plastic, Airway management in cleft lip and palate surgery, HATCH, D. J., (*E*) 755–756
——, Difficult laryngoscopy in cleft lip and palate surgery, GUNAWARDANA, R. H. 757–759
——, Regional anaesthesia for outpatient nasal surgery, MOLLIEX, S., *et al.* 151–153
Surgery, thoracic, Absence of an early pre-emptive effect after thoracic extradural bupivacaine in thoracic surgery, AGUILAR, J. L., *et al.* 72–76
——, Continuous extrapleural paravertebral infusion of bupivacaine for post-thoracotomy analgesia in young infants, KARMAKAR, M. K., *et al.* 811–815
——, Does propofol change the phenotype of monocytes in thoracic surgery? LAẞNIGG, A., *et al.*, (*EACTA*) A.18
Surgery, vascular, Aortic stent surgery, BARANOWSKI, A. P., *et al.*, (*C*) 882–883
——, Aortic stent surgery, THOMPSON, M. M., *et al.*, (*C*) 883
——, Delayed forced air warming prevents hypothermia during abdominal aortic surgery, KARAYAN, J., *et al.* 459–460
——, Preoperative inhibition of angiotensin-converting enzyme improves systemic and renal haemodynamic changes during aortic abdominal surgery, LICKER, M., *et al.* 632–639
——, Rheological properties of commonly used plasma substitutes during preoperative normovolaemic acute haemodilution, FREYBURGER, G., *et al.* 519–525
Surgery, ventilatory response, Effects of surgical skin incision on respiration in patients anaesthetized with enflurane, SUTHERLAND, R. W., *et al.* 777–779
Survey, Echocardiography by the anaesthetist: a French survey, LEHOT, J. J., *et al.*, (*EACTA*) A.43
Sympathetic nervous system, adrenergic block, A comparison of the limitation of sympathetic responses by β_1-blocker esmolol and α_2-adrenergic agonist dexmedetomidine, WILLIGERS, H. M. M., *et al.*, (*EACTA*) A.23
——, Antinociceptive actions of intrathecal xylazine: interactions with spinal cord opioid pathways, GOODCHILD, C. S., *et al.* 544–551
Sympathetic nervous system, catecholamines, Early effects of total hepatectomy on haemodynamic state and organ uptake of catecholamines in the pig, JAMES, M. F. M., *et al.* 713–720
——, Methylprednisolone inhibits endotoxin-induced depression of contractile function in human arteries *in vitro*, TSUNEYOSHI, I., *et al.* 251–257
Sympathetic nervous system, clonidine, Extradural analgesia in the first stage of labour, BUGGY, D., *et al.*, (*C*) 887
——, Extradural analgesia in the first stage of labour, FERNANDO, R., *et al.*, (*C*) 886–887
——, Extradural analgesia with clonidine and fentanyl compared with 0.25% bupivacaine in the first stage of labour, BUGGY, D. J., *et al.* 319–321
——, Extradural clonidine for postoperative pain relief, COOK, B., *et al.*, (*C*) 881
——, Extradural clonidine for postoperative pain relief, NISHIKAWA, T., (*C*) 171
——, Extradural clonidine for postoperative pain relief, NISHIKAWA, T., (*C*) 881–882
——, Influence of oral clonidine on the ventilatory response to acute and sustained isocapnic hypoxia in human males, FOO, I. T., *et al.* 214–220
——, Spinal clonidine produces less urinary retention than spinal morphine, GENTILI, M., *et al.* 872–873
Sympathetic nervous system, dopamine, Effect of low-dose dopamine on intestinal villus microcirculation during normotensive endotoxaemia in rats, SCHMIDT, H., *et al.* 707–712
Sympathetic nervous system, dopexamine, Effects of dopamine and dopexamine on splanchnic microcirculation during major surgery in humans, BELLAMY, M. C., *et al.*, (*ARS*) 587P
Sympathetic nervous system, esmolol, A comparison of the limitation of sympathetic responses by β_1-blocker esmolol and α_2-adrenergic agonist dexmedetomidine, WILLIGERS, H. M. M., *et al.*, (*EACTA*) A.23
Sympathetic nervous system, lidoflazine, Effects of lidoflazine on left ventricular function, DEIRUE, G. L., *et al.*, (*EACTA*) A.10
Sympathetic nervous system, metaraminol, Hypotension during subarachnoid anaesthesia: haemodynamic effects of colloid and metaraminol, CRITCHLEY, L. A. H., *et al.* 734–736
Sympathetic nervous system, xylazine, Antinociceptive actions of intrathecal xylazine: interactions with spinal cord opioid pathways, GOODCHILD, C. S., *et al.* 544–551

Temperature, A comparison of core temperature with thermal energy balance in predicting adequacy of rewarming from hypothermic cardiopulmonary bypass, Deakin, C. D., *et al.*, (*EACTA*) A.41
——, Continuous temperature and O_2 saturation monitoring of jugular blood during DHCA procedures for aortic surgery, Paino, R., *et al.*, (*EACTA*) A.40
Temperature, body, Convective warming combined with vasodilator therapy accelerates core rewarming after coronary artery bypass surgery, Harrison, S. J., *et al.* 511–514
——, Perioperative inadvertent hypothermia: what do we need to prevent? Carli, F., *et al.*, (*E*) 601–603
——, Preoperative infusion of amino acids prevents postoperative hypothermia, Selldén, E., *et al.* 227–234
Temperature, effect, Elevated serum levels of S-100 after deep hypothermic circulatory arrest correlate with duration of circulatory arrest, van der Linden, J., *et al.*, (*EACTA*) A.84
Temperature, metabolism, Preoperative infusion of amino acids prevents postoperative hypothermia, Selldén, E., *et al.* 227–234
Temperature, monitoring, Convective warming combined with vasodilator therapy accelerates core rewarming after coronary artery bypass surgery, Harrison, S. J., *et al.* 511–514
——, Delayed forced air warming prevents hypothermia during abdominal aortic surgery, Karayan, J., *et al.* 459–460
——, Perioperative inadvertent hypothermia: what do we need to prevent? Carli, F., *et al.*, (*E*) 601–603
——, Use of i.m. temperature probes during cardiopulmonary bypass in humans, Benson, J. P., *et al.*, (*C*) 472
——, Use of i.m. temperature probes during cardiopulmonary bypass in humans, Manners, J. M., (*C*) 471–472
The ABC of Resuscitation, 3rd Edn, Colquhoun, M. C., *et al.*, (editors), (*R*) 338–339
Theories of anaesthetic action, molecular, Voltage-sensitive Ca^{2+} channels and anaesthesia, Hirota, K., *et al.*, (*E*) 344–346
Therapy, Does perioperative transoesophageal echocardiography change the therapy of cardiothoracic patients? Brase, R., *et al.*, (*EACTA*) A.47
Thrombus, pulmonary, Minimal incidence of reperfusion pulmonary oedema after pulmonary thromboendarterectomy, Mares, P., *et al.*, (*EACTA*) A.75
Transfusion, Consensus statement on autologous transfusion, Royal College of Physicians of Edinburgh, 470
Transfusion, autotransfusion, Consensus statement on autologous transfusion, Royal College of Physicians of Edinburgh, 470

Understanding Anaesthesia, 3rd Edn, Carrie, L. E. S., *et al.*, (*R*) 892–893

Veins, Effects of propofol on rabbit mesenteric arteries and veins, Kamitani, K., (*C*) 333–334
——, Effects of propofol on rabbit mesenteric arteries and veins, Stratford, N., (*C*) 333
Ventilation, Non-invasive pressure support ventilation (NPSV) as an alternative to reintubation, Paulus, S., *et al.*, (*EACTA*) A.73
Ventilation, apnoea, A model to describe the rate of oxyhaemoglobin desaturation during apnoea, Farmery, A. D., *et al.* 284–291
——, A model to describe the rate of oxyhaemoglobin desaturation during apnoea, Farmery, A. D., *et al.*, (*e*) 890
Ventilation, carbon dioxide response, Carbon dioxide output in laparoscopic cholecystectomy, Kazama, T., *et al.* 530–535
——, Ventilatory response to carbon dioxide, Dahan, A., *et al.*, (*C*) 747
——, Ventilatory response to carbon dioxide, Saito, Y., *et al.*, (*C*) 747–748
Ventilation, deadspace, Carbon dioxide output in laparoscopic cholecystectomy, Kazama, T., *et al.* 530–535
Ventilation, effects, Effects of surgical skin incision on respiration in patients anaesthetized with enflurane, Sutherland, R. W., *et al.* 777–779
Ventilation, high frequency jet, Airway pressure signals during high frequency jet ventilation, Lin, E. S., (*ARS*) 576–577P
Ventilation, hyperventilation, Slow ventilatory dynamics after isocapnic hypoxia and voluntary hyperventilation in humans: effects of isoflurane, Dahan, A., *et al.* 374–381
Ventilation, hypoxic response, Influence of oral clonidine on the ventilatory response to acute and sustained isocapnic hypoxia in human males, Foo, I. T., *et al.* 214–220
——, Slow ventilatory dynamics after isocapnic hypoxia and voluntary hyperventilation in humans: effects of isoflurane, Dahan, A., *et al.* 374–381
Ventilation, mechanical, Volumetric analysis of aeration in the lungs during general anaesthesia, Reber, A., *et al.* 760–766
Ventilation, pattern, Effects of surgical skin incision on respiration in patients anaesthetized with enflurane, Sutherland, R. W., *et al.* 777–779
Ventilation, positive end-expiratory pressure, Systolic pressure variation—a way to recognize dynamic hyperinflation, Myles, P. S., (*C*) 169
——, Systolic pressure variation—a way to recognize dynamic hyperinflation, Perel, A., *et al.*, (*C*) 168–169
Vomiting, antiemetics, Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting, López-Olaondo, L., *et al.* 835–840
——, Comparison of ondansetron and prochlorperazine f[illegible] prevention of nausea and vomiting after adenotonsillectomy, van den Berg, A. A. 449–45[illegible]
——, Effect of ondansetron on nausea and vomiting [illegible] middle ear surgery during general anaesthesia. Honkavaara, P. 316–318
——, Effect of transdermal hyoscine on nausea ar[illegible] Foster, R. N., (*C*) 749
——, Effect of transdermal hyoscine on nausea ar[illegible] Honkavaara, P., (*C*) 749–750
——, Effect of transdermal hyoscine on nausea and [illegible] during and after middle ear surgery under local anaesthesia, Honkavaara, P. 49–53
——, Interaction of i.v. anaesthetic agents with 5-HT_3 receptors, Appadu, B. L., *et al.* 271–273
——, Prevention of vomiting after paediatric strabismus surgery, Morton, N. S., (*C*) 473
——, Prevention of vomiting after paediatric strabismus surgery, Tramèr, M., *et al.*, (*C*) 473–474
——, Single dose i.v. tropisetron in the prevention of postoperative nausea and vomiting after gynaecologica[illegible] surgery, Capouet, V., *et al.* 54–60
——, Single-dose i.v. granisetron in the prevention of postoperative nausea and vomiting, Wilson, A. J., *et al.* 515–518
Vomiting, incidence, Prediction of postoperative nausea and vomiting using a logistic regression model, Toner, C. C., *et al.* 347–351
Vomiting, nausea, Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting, López-Olaondo, L., *et al.* 835–840
——, Comparison of ondansetron and prochlorperazine for the prevention of nausea and vomiting after adenotonsillectomy, van den Berg, A. A. 449–451
——, Effect of ondansetron on nausea and vomiting after middle ear surgery during general anaesthesia, Honkavaara, P. 316–318
——, Effect of transdermal hyoscine on nausea and vomiting, Foster, R. N., (*C*) 749
——, Effect of transdermal hyoscine on nausea and vomiting, Honkavaara, P., (*C*) 749–750
——, Effect of transdermal hyoscine on nausea and vomiting during and after middle ear surgery under local anaesthesia, Honkavaara, P. 49–53
——, Interaction of i.v. anaesthetic agents with 5-HT_3 receptors, Appadu, B. L., *et al.* 271–273
——, Nausea and vomiting after cardiac surgery, Grebenik, C. *et al.*, (*EACTA*) A.76
——, Omitting nitrous oxide in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials, Tramèr, M., *et al.* 186–193
——, Prediction of postoperative nausea and vomiting using a logistic regression model, Toner, C. C., *et al.* 347–351
——, Single dose i.v. tropisetron in the prevention of postoperative nausea and vomiting after gynaecological surgery, Capouet, V., *et al.* 54–60
——, Single-dose i.v. granisetron in the prevention of postoperative nausea and vomiting, Wilson, A. J., *et al.* 515–518
Vomiting, nausea, anaesthetic factors, Omitting nitrous oxide in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials, Tramèr, M., *et al.* 186–193
——, Prediction of postoperative nausea and vomiting using a logistic regression model, Toner, C. C., *et al.* 347–351
Vomiting, nausea, surgical factors, Prediction of postoperative nausea and vomiting using a logistic regression model, Toner, C. C., *et al.* 347–351

Wylie & Churchill-Davidson's A Practice of Anaesthesia, 6th Edn., Healy, T. E. J., *et al.*, (editors), (*R*) 477